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ASIATIC SCHISTOSOMIASIS

the Result of Infection by the Blood-worm

SCHISTOSOMA JAPONICUM.

Thesis for the Degree of M.D.

by

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1915

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CONTENTS.

	page.
Introduction	1
Definition	2
History	3
Geographical Distribution	8
The Natural History of the Parasite	13
The Miracidium	20
Infection of Man	26
Etiology	44
Pathology	47
Resumé of Pathology	70
Clinical Features	76
Summary of Signs and Symptoms	97
The Blood	105
Schistosomiasis in Animals	110
Diagnosis	114
Prognosis	119
Treatment	122
Prophylaxis	1[illegible]
Conclusions	1[illegible]
Bibliography	1[illegible]

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SCHISTOSOMA JAPONICUM.

Introduction.

It is my desire, in this Thesis, to present as complete a picture as possible of our present-day knowledge of the disease which is caused by the infection of the human body by the Trematode worm, Schistosoma japonicum.

My interest in this particular verminous infection dates back to November 1907, when I first discovered the ova of this parasite in the course of the clinical examination of one of my patients. Fourteen years residence in Central China has given me the opportunity of studying a number of most interesting tropical conditions, but none of these have interested me more than the one which it is my purpose to discuss - the invasion of the human host by the blood parasite in question.

Helminthiasis in China.

Systematic microscopical examination of the faeces of my hospital in-patients soon convinced me that helminthic affections abound in China. With the idea of ascertaining to what extent verminous infections were prevalent among the general population in my district, I examined the stools of 150 consecutive and entirely unselected cases coming to the hospital. The result showed that 137 out of the 150, or 91.3%, harboured intestinal parasites. The worms most commonly present/

present were Ascaris lumbric., Trichocephalus dispar, Ankylostom. duodenale, and Oxyuris vermicularis. Besides the above mentioned Nematodes, various species of Cestodes and Trematodes are prevalent in many parts of China, though in the province of Hunan I did not find them so generally distributed as the nematode worms. With regard to the trematode worm Schistosoma japonicum, though it has a wide geographical distribution, it occurs essentially in endemic areas where the conditions are suitable for its propagation. In these endemic foci quite a large percentage of the male population may be infected, though outside such localities the general populace may suffer but little, if at all. The geographical range which includes these infected districts, however, is so extensive, not only in China but in the far East generally, and the disease itself is so terrible, both on account of the acute suffering and the high mortality which it causes, that the subject of Asiatic Schistosomiasis becomes one of very great importance.

Definition.

The disease may be defined as a chronic endemic disease of Eastern Asia, caused by the entrance into the body of a blood parasite, Schistosoma japonicum. This parasite by its own obstructive and irritative presence in the blood vessels, by the deposition of numberless eggs in the tissues, and by the elaboration of a toxin, causes/

causes a very grave pathological condition, which is characterised by marked cirrhosis of the liver, ascites, dysenteric symptoms, progressive anaemia, and great weakness. In cases of severe infection the disease progresses to a fatal termination.

History.

The blood-fluke, Schistosoma japonicum, was first discovered in April 1904 by Professor Katsurada of Okayama, in Japan. The disease caused by this parasite had, however, been recognised by Japanese physicians for some years previous to this date. It occurred in certain endemic localities in the provinces of Bingo, Yamanashi, Hiroshima, and Saga, and was popularly known as the "Katayama disease", Katayama being the name of a heavily infected centre in Bingo. The disease was of a readily recognised type, for it was characterised by enlargement of the liver and spleen, dysenteric symptoms, ascites, cachexia, and a high mortality. The cause of this disease was not understood, although as long ago as 1887 Majima wrote of a peculiar form of liver cirrhosis caused by an unknown parasite, and certain other observers (Yamagiwa, 1890; Kurimoto, 1893; Fujinami, 1904) had found the ova of an unrecognised worm in various organs, especially the liver, in cadavers coming from infected districts.

In 1904 Katsurada made a special study of the disease in the Yamanashi province. In the faeces of five out of fifteen patients, suffering from the malady, he/

he discovered ova somewhat resembling the ova of the African blood-fluke, Schistosoma haematobium, and he strongly suspected that the disease was due to another and probably closely allied trematode worm. As Katsurada was unable to obtain an autopsy, he procured some cats and dogs from an infected district and dissected these in the hope of finding the worm, having before noticed that certain of the trematodes which infected man in Japan, notably Paragonimus westermanii and opisthorchis sinensis, were also frequently to be found in the cats and dogs of the endemic area. In this he was successful, for systematic examination of these animals resulted in the discovery of many adult worms of a new species of blood-fluke in the portal and mesenteric veins of a cat, besides numerous eggs in the liver and walls of the large intestine. This new species, together with the eggs he had found in man, Katsurada fully described in a Japanese paper in August 1904, and, owing to the resemblance of the worm to the well-known African species, Schist. haematob., as well as the resemblance between the eggs of the two variations in that both contained a myracidium, he proposed for this newly discovered parasite the name of Schistosoma Japonicum. In December 1904 he published another article on this subject in German[1], and in this he states that Fujinami had announced the discovery in October 1904 of a female specimen of Schist. jap. in a human subject.

A little later in the same year Dr. John Catto, then resident medical officer at the quarantine station in Singapore, independently discovered the eggs of this worm in sections taken from the liver, mesenteric glands, and intestines of a Chinese (Fukien province) who had died of cholera. Catto, in the first instance, took these eggs to be coccidia, and the case was originally published as one of coccidiosis in man. Further study of his material in London, however, revealed the presence in the tissues, notably in the mesenteric blood vessels, of adult trematodes, and he thus came to the conclusion that the peculiar oval bodies which, at the outset, he had taken to be coccidia were in reality the ova of this parasite. He therefore presented a paper before the British Medical Association at Oxford (July 26-29, 1904) claiming a new species of trematode for man, and this was published in the British Medical Journal, September 7th, 1904. He did not, however, either name the parasite or minutely describe it, but Blanchard, to whom Sir Patrick Manson had sent some of Catto's slides, recognised the specimens as representing a new species of blood fluke, and to this new species he gave the name of S. Cattoi. Under this name, therefore, Catto published another article[2] in January 1905, in which he more fully described the parasite. Stiles also, who had the opportunity (September 1904) of examining Catto's material in London, was able definitely to satisfy himself that the new worm was not S. haematobium. At a

later/

later date, careful comparison of the Japanese and Chinese varieties, as described by Katsurada and Catto respectively, convinced Stiles[15] that these two were in reality one and the same species. Thus it became evident that besides the African blood-fluke, S. haematobium, the well-known cause of Bilharziasis in man, there existed yet another and specifically distinct Asiatic species of trematode worm, which, like the older variety, was also a parasite of the human blood-vessels. Subsequent study very soon and very completely established the truth of these earlier observations.

The second case from China was reported by Dr. O. T. Logan in June 1905. It was encountered in his hospital practice in Chang-teh, North-west Hunan, Central China. Logan sent specimens of faeces, containing eggs of S. japonicum, to Dr. H. G. Beyer, Medical Inspector, U.S. Navy. Beyer (in association with Stiles, who was in possession of one of Catto's original preparations) recognised the egg as undoubtedly that of S. japonicum, and as it represented the second case from China, and as it indicated a new locality for the parasite, he published his notes of the case in September 1905, under the heading "A second Chinese Case of Infection with the Asiatic Blood Fluke (Schist. japonic.)."[16]

I must myself have been brought into contact with cases of Katayama disease even as early as 1900.[17] At that time I was engaged in hospital work, of a decidedly pioneering/

pioneering character, in the city of Yo-chow, North Hunan. The town is situated at the North-East corner of the Tung-ting lake, just where the lake empties itself into the Yang-tse-kiang. The disease is endemic in all the country-side round about Yo-chow, indeed the district may be described as a perfect hot-bed of the trouble. In those early days I had not the facilities for clinical investigation or the necessary means for distinguishing the different tropical conditions, which I afterwards enjoyed, and thus the origin of the trouble escaped me. In 1905 I moved still further inland, travelling up the Siang river (one of the great tributaries of the Yang-tse) till I reached Heng-chow, a large city situated in the Southern part of the province. Here I was enabled, in the course of time, to erect a modern hospital, more fully equipped, and with better opportunities for investigating and treating the diseases incident among the people. It was not until 1907, therefore, as already mentioned, that, owing to increased laboratory facilities, I was in a position to make definite microscopic diagnosis of the cause of this trouble.

My first three cases were published in the Journal of Tropical Medicine[5] in March 1909, and this constituted one of the first reports of Schist. japonicum infection from China; though in 1906 Woolley[6] reported a case from the Philippine Islands. In this paper I endeavoured to give as complete a picture of the clinical features of the affection as possible, more particularly for the reason that:

that hitherto nothing had appeared, in English at any rate, which gave anything like a full description of the symptomatology of the disease.

Since that time the disease has been recognised many times by many observers. Once it had been fully described, and the method of diagnosis by means of the microscope made plain, it was speedily reported from many parts of the Yang-tse valley. Indeed it soon became evident that the parasite had a wide distribution, and not only so, but that in the endemic areas in which it occurred, this verminous infection was responsible for an appalling amount of sickness and suffering, and for a very high mortality.

Geographical Distribution.

The geographical distribution of S. japonicum covers a very wide area. The parasite is found to occupy large tracts of country throughout Central China, and it occurs also in Japan and the Philippine Islands. Within these limits, and wherever the conditions are favourable for development and propagation, it flourishes exceedingly. These conditions include a high Summer temperature, with humidity of atmosphere, level country, and plenty of surface water. Where these are present the worm finds that environment which is suitable for its embryonic and extra-corporeal life, and that opportunity for effecting an entrance into its future host which is essential to its parasitic life. In those localities where,

where the environment is unfavourable, especially where the country is hilly and not under cultivation, and where water cannot collect in any quantity, this trematode worm is not to be found, nor are the inhabitants of such places found to be infected. Hence it is that though the disease caused by this parasite is distributed over a very wide area, it occurs essentially in endemic patches, some large, some circumscribed, within that area. Moreover, the intensity of the infection, as shown by the percentage of the population affected, varies very considerably in the different endemic foci, and this variation has reference to the local conditions, being dependant on the suitability of the environment as regards the nature of the country, the amount of water present, and the extent of swampy land under cultivation.

The distribution of the parasite in China follows, in the main, the low-lying plains of the provinces which border on the great Yang-tse-kiang, and on its tributaries. Here we find the conditions peculiarly favourable for its life and growth. The climate, which may be described as sub-tropical, is very hot and steamy during the summer months (mean maximum daily temperature about 90°F. in the shade), and the rain-fall is heavy. Extensive tracts of flat low-lying land, inundated with overflow water, border on the full river, into which also numerous tributaries and creeks empty themselves. Rice is very extensively cultivated in these regions, forming, as it does, the staple food of the people. In the warm early

Summer it is planted out in the flooded fields by the farmers, who wade bare-legged in the water and plant the rice-tufts by hand. This, as we shall have cause to refer to again, is a fruitful source of infection. In addition to the rice or "paddy" fields, innumerable shallow lakes and ponds are to be found, whose stagnant waters, warmed up by the fierce rays of the tropical sun, form ideal culture-beds for the parasite. Thus we find that the conditions essential to the parasite's life, viz., a high summer temperature, low-lying country, and the existence of abundance of water, are ideally fulfilled in many and extensive regions in the Yang-tse Valley, and these same conditions of necessity obtain in the infected localities in the Philippine Islands and in Japan.

In China the provinces which have been reported to be infected are:- Hunan, Hupeh, Honan, Kiangsi, Anhuei, Kiangsu, Chekiang, Fukien, and Kwang-tung - practically the whole central basin of the Yang-tse. It has not, so far, been reported from the Western Province of Szechuan, through which also the Yang-tse flows. It may yet be discovered there, indeed I think this to be highly probable, though, owing to the more mountainous character of the country, the endemic areas would be less extensive and more widely scattered. The parasite is not to be found in North China, where the climate is altogether different from that of the South,

being/

being very much cooler and very dry. The character of the soil in the North is sandy and porous, and instead of rice, crops of wheat, maize, and millet are raised from a dry soil.

As regards the Yang-tse provinces, those most heavily affected would appear to be Hunan, Hupeh, Kiang-si, An-huei, and Kiang-su. In Hunan there are some very heavily infected areas, notably the country round about the Tung-ting lake, just South of the Yang-tse. In Hupeh, Wills[7] reports the prevalence of the infection among the fishers and lake-side dwellers near the lakes to the East of the province and North of the river. In Kiang-si, Lambert[8] has reported that the country back of Kiukiang, which is on the river, is very heavily infected. Houghton reports that all cases coming to the hospital from a certain place in the Kiukiang district were infected. In An-huei, Houghton[9], who was for some years stationed at Wuhu, reports that the parasite is practically limited to the rice-growing divisions of the province, that is, the Southern half, which is very heavily infected. He states that during 1909, 8% of all male cases entering the Wuhu general hospital showed infection, latent or overwhelming. Most of these cases came from two heavily infected foci of the disease, the patients coming from these parts asserting that one out of every three or four of the farmers and boatmen were seriously ill from the trouble. From one particularly

pestilential/

pestilential spot, Lohsing, every patient who applied to the hospital for treatment, for whatever malady, was found infected. The coast province of Kiang-su, through which the Yang-tse runs to the sea, is affected in like manner. Jeffreys has reported the North of Chekiang also as heavily infected. He states that in the country round about Kashing, S. japonicum is a perfect scourge to the inhabitants, whole villages being decimated. The amount of sickness and the high mortality caused by this parasitic worm endemic in these Yang-tse provinces is truly appalling.

Under very much the same climatic conditions this trematode is to be found in the Philippine Islands and Japan. In the endemic areas the same conditions obtain as in China; thus we have the flooded plains given up to the cultivation of rice, the numerous water-ways and lakes, the heavy rain-fall, and the high summer temperature. The reports from the Philippine Islands[2-6] indicate that the Southern islands of Lamar, Leyte, and Mindanas, are those mainly implicated. In Japan, the Provinces chiefly affected are Bingo, Yamanashi, Hiroshima, and Saga.

Much work remains to be done to determine more precisely the distribution of this dangerous parasitic worm, and there can be but little doubt that, as time goes on, the geographical area involved will be found to be more widely extended than is at present supposed.

The Natural History of the Parasite.

Schistosoma japonicum belongs unquestionably to the Trematode order of the Platyhelminthes. Comparison with S. haematobium reveals such outstanding points of similarity that there can be no difficulty in placing it at once in the Family of Schistosomidae. The two Species are similar in general morphology, and also in that males and females are found in pairs, the elongated and slender female lying in the gynecophoric canal of the male. The sexes are necessarily apart when young, but pair off when mature. The main points which distinguish S. japonicum from S. haematobium are the smaller size of the former, the relatively large size of its posterior sucker, and the smooth body of the male worm. The eggs also are a little smaller, and of a somewhat different shape, in S. japonicum, and other differences exist in intestine and vitellogene glands, but the foregoing are sufficient to establish the two forms as entirely distinct.

The following table will give in fuller detail the differences which exist between the two species.

(Comparison.)

Comparison of S. japonicum with S. haematobium.

S. Japonicum.[1]	S. haematobium.[10]
Male.	**Male.**
Length, 7-12 mm. Aver. 10.5 Breadth, Aver. .5 mm. Colour, Dirty white	Length 1 cm. Whitish.
Body, Flat, caudal end tapers. Mouth, funnel shaped, .2 mm. Acetabulum, pedunculate. A little larger than oral sucker.	Body tapers at each end. Oral and ventral suckers one behind the other.
Form folds over and forms a gynecophoric canal, surface of which is provided with minute spines, similar to those on suckers but not so numerous.	Form also flattened as a leaf, but lateral parts fold over and overlap, forming gynecophoric canal.
Dorsally, no spinous warts.	Dorsally, covered with spinous warts, or small tubercles.
Oesophagus, simple, bifurcates into two intestinal caeca.	
Caeca unite sooner or later to form median stem. May separate again, once or several times.	Same, point of union usually more anterior.
Testicles, usually six in number, and close together, lobular, vesiculae sem. present. Vas deferens comparatively long.	Vas deferens shorter than in S. japonicum.
Genital pore, closely posterior to acetabulum, at entrance of gynecophoric canal.	
Excretory pore, dorso-terminal.	
Female.	**Female.**
Length, 8-12 mm. (sometimes longer)	Length, 2 cm.
Colour, dirty. Caudal half dark, nearly black, owing to vitellog. glands, and because of blood in the intestine.	Colour, Upper part white. Lower half grey, with dark zig-zag stripe due to intest. canal filled with blood.
Shape, almost cylindrical, more slender than male. Greatest/	Same.

S. Japonicum.	S. haematobium.[10]
Female.	Female.
Greatest thickness, .4 mm., anterior and posterior end pointed.	
Suckers, Oral sucker circular, .01 mm., provided with minute spines. Anterior and posterior suckers approached, posterior larger than anterior.	Suckers, Anterior sucker larger than posterior.
Integument, smooth.	Same.
Excretory pore, terminal. Excretory apparatus well dev^{d}. Similar to that of S. haemat.	
Oesophagus, branches into two intestinal caeca, which unite behind ovary to form median canal. This runs in zig-zag course to tail. Median stem thicker than in S. haemat., and contains brown pig^{t}. and leucocytes.	Median stem more slender.
Ovary, elongated oval, .59 mm. in a worm 11.5 mm. long, and .39 mm. in one of 8 mm.	Ovary; bulging in region of ovary, less marked than in S. japonicum.
Oviduct begins at caudal end of ovary, turns and runs forward and unites with vitelline duct in front of ovary. Here empty the shell glands. Ootyp present.	
Uterus, central and elongated, extends in the median field occupying anterior half of the body to genital pore, which is directly behind the acetabulum.	Uterus does not extend into anterior half of body.
Ova are arranged irregularly in single or double rows.	

The Ovum.

The ova of S. Japonicum are frequently passed in large numbers from the intestinal canal of a patient afflicted,

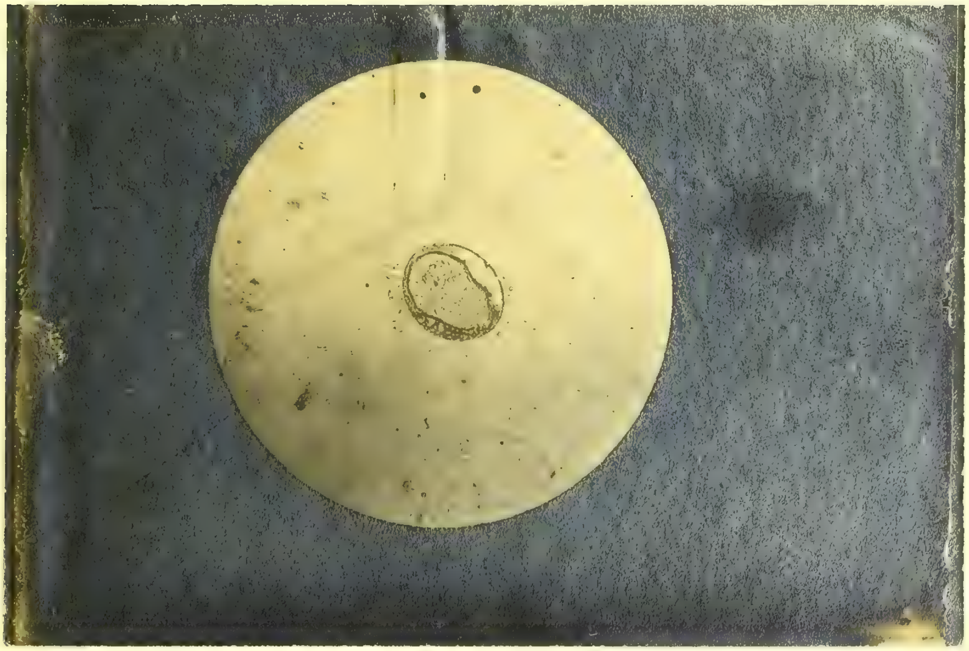
afflicted with Asiatic Schistosomiasis. On first finding the egg one cannot fail to be struck by its characteristic appearance, marking it as entirely distinct from all other verminous ova. Catto, in his original article, remarks that "probably the ova had been found many times" (i.e. previous to his own discovery of the eggs post-mortem), "in the course of ordinary microscopical examinations of faeces, but had been mistaken for the ova of ankylostom. duodenale which they closely resemble." The eggs are, in reality, totally different and distinct from those of the ankylostome, and could not be mistaken for them by any observer using reasonable care. Others also, authorities to whom specimens have been forwarded have, like Catto, described the egg quite erroneously, both as regards its appearance and measurements, and I have no doubt that these entirely wrong descriptions are to be accounted for by the fact that they were made from preserved and not from fresh specimens. Ova, in a preserved state, have invariably shrunk, appear to have a thick shell, and show none of the characteristic appearances presented by eggs containing a living and moving embryo.

I fully described the egg in my article published in the Journal of Tropical Medicine in March 1909[1]. In that paper I said:-

"On first finding the egg, by a process of exclusion, one quickly arrives at the conclusion that it must be that of S. japonicum. It is evidently not one of the common,

common varieties of ova met with in the stools (Ascaris, Tricocephalus, Ankylostom.). It is plainly not a Cestode egg. One is forced to the conclusion that it must be that of a Trematode. But one remembers that all the trematode eggs are operculated, except those of the Schistosoma. Therefore as this egg is not operculated, it must be either S. haematobium or S. japonicum. That point, however, is decided at a glance, for the egg of S. haematobium is spiked, either terminally or laterally, and as in this egg we have no trace of a spine, but a perfectly clear smooth shell, we reach the conclusion that we are dealing with a case of infection by S. japonicum.

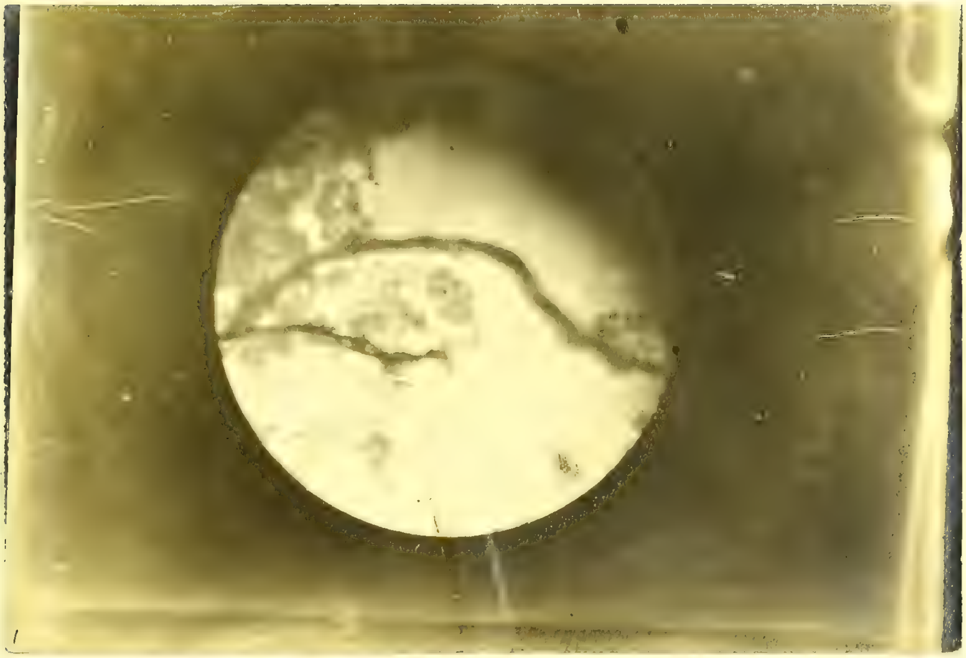
"On the first occasion that I saw the ovum I had mounted a specimen of the faecal matter in a drop of plain water in the ordinary way. With a ⅙" objective one saw at once a number of large oval eggs with granular contents, unoperculated, unspiked, smooth, transparent, and showing clearly a double outline. On returning to the specimen an hour or two after I had mounted it, and finding the water drying up from under the coverglass, I added another drop. Almost immediately after applying the drop of fresh water I found that the eggs began to hatch out. The shell simply ruptured and a free-swimming ciliated miracidium escaped, and by means of its cilia would swim gracefully across the field. The shape of the embryo, as I saw it, resembles



resembles somewhat that of Fasciola hepatica, but the papilla is not so sharp. This differs from the description given by Logan who . . . describes the free-swimming embryo as being 'melon-seed shaped', and drew it after that manner.

"Using 1/6" objective and a micrometer I carefully measured the egg a number of times, and found that, though it varied considerably, the average size was .1 mm. long by .07 mm. broad. To prove that there was no error in the measuring, an ankylostome egg was also measured by the same method and the results found to agree with the dimensions given in the text books for the ovum of that parasite. It was thus found that the egg of S. japonicum was often nearly twice that of A. duodenale. I mention this because the measurements given in the volume on Tropical Diseases in Allbutt's System do not correspond with what I found. In the few notes given on S. japonicum in the above volume, the eggs are stated to be between 0.06 and 0.09 mm. in length, and .03 to .05 mm. in breadth, which makes the egg to be only equal in length to the breadth of the ovum as I found it.

"There is another difference. The eggs are described as having 'a stout, smooth shell'. Smooth certainly but not stout. On the contrary, the shell is very thin and delicate, and easily ruptures. In mounting specimens one has to be careful not to exert any undue pressure on the cover-glass, or to slide it along/



along the glass slip, otherwise the shell will be found broken.

"In order to confirm the diagnosis of my first cases, I sent specimens to Sir Patrick Manson, who wrote in reply that he had 'very little doubt' that they contained eggs of S. japonicum. He says 'the size, shape, colour, ciliated embryo in a non-operculated shell all point to this . . . . The shape of the ciliated embryo goes for little, as their bodies are very plastic, and assume many forms according as to how they are travelling.' . . . . As already stated, the egg under 2/3" objective is seen to be quite clear and not stained by the bile. It is oval, transparent, and shows a very clear double outline. When using the higher power (1/6" obj.) one sees at once that the double contour is due to the single clear outline of the egg-shell on the outside, and within this, also quite clearly defined, the outline of the embryo. The embryo, evidently a living ciliated miracidium, occupies practically the whole length of the egg, though at the sides there is some little space between the outline of the embryo and that of the shell. In this space more or less granular material is to be found. At what is evidently the head-end of the embryo there is always a distinct rostrum or papilla. The internal structure cannot be made out very plainly, being granular and ill-defined."

In/

In the ova taken from a freshly-passed stool the embryo is usually quiescent. The first movement to be detected is usually a circumscribed rotatory movement in two small areas, anterior and posterior. Next, ciliary movement can be seen in the cilia covering the body, and various subtle and indefinite changes are constantly going on in the protoplasm of the interior. Then the head-end shows lively twisting movements and, finally, general body movements of the embryo within its shell. I give some drawings which I made from actual specimens, and they will, I think, give a truer idea of the appearances presented than any further description.

The Miracidium.

The miracidium will only emerge from the egg in the presence of water, which is absolutely essential to its life and development. When hatched it is seen through the microscope to be a graceful little creature which moves about with great freedom and activity. It is difficult, under artificial conditions, to keep it alive for long, usually not more than a day or two, but Houghton says that he has managed to keep the embryos alive for five days by changing the water daily. The shape usually assumed is somewhat oval, with protruding proboscis-like structure. According to Logan the embryo is "the shape of a melon seed". The body is ciliated all over but the cilia are specially long and active at the anterior end, about the "neck". When they

the embryo is in the shell the cilia show like small pigment granules, but when out of the shell they appear as lashes which project from the body at different angles, depending on their location. It is difficult to give a clear description of the internal organs, as they show up very indistinctly. There is, as Stiles[12] says, a yellow, highly-refractile, "gastric-sac" at junction of the first and second thirds, and this is in connection with the anterior protuberance; but the two large head-glands seen in S. haematobium are not observed in this species.

To return to the Ova, in March 1911 Dr. Leiper, Helminthologist of the London School of Tropical Medicine, announced that these were in reality spined, notwithstanding the numerous descriptions of the egg by writers in the far East who had unanimously described the egg as destitute of any trace of a spine. Faecal specimens obtained from a dog and containing S. japonicum ova were sent to Leiper from Hankow, and, on examining the material he found that the eggs presented "a curious little nipple-like knob or spine situated a short distance from one of the poles of each egg". He then examined Catto's original specimens, and other material from two human cases in China, and was able to confirm the presence of the spine. It was sometimes difficult to find, but, by careful movement, so as to roll the egg under the cover-glass, it could ultimately be brought to light.

An/

As the result of an examination of about fifty eggs from seven different cases, four from man and three from dogs, Leiper came to the conclusion that "the schistosome found in the dog is of the same species as that found in man, and that the S. japonicum is characterised normally by the presence of a small knob-like cuticular spine". This observation was confirmed by Sambon, who describes it as "a small nipple-like spine protruding from the centre of a saucer-like depression near the posterior pole of the egg". The presence of this small blunt spine in the egg of S. japonicum was regarded by Leiper as of importance as permitting a definite diagnosis of this species.

After the appearance of Leiper's notes describing this "spine", I took special pains to verify the matter for myself. Careful examination of the eggs in my next case soon convinced me of the accuracy of Leiper's findings. The "spine", in reality, is a very small curved nipple-like projection towards one pole of the egg, and often requires some searching for. Frequently it is not seen at all as the egg is lying so as to conceal the spine on its under surface. I reproduce here some rough drawings of the eggs which I made in that case, and which, together with some notes, I published in the China Medical Journal, November 1915[11]. The drawings here given show also an abnormal type of schistosome egg which I took to be the unfertilised ovum of/

of the worm. "These contained no miracidia", to quote from the article referred to, "but were filled with globular material. They were smaller than the fertilized eggs, being about the same size as the ova of Ankylostom. duodenale, very slightly bile-stained, and showing a single sharp outline, in contra-distinction to the double outline in the ordinary embryo-containing egg. In both fertilized and unfertilized ova the little curved nipple or spine could usually be found towards one pole."

It is strange that other observers have found difficulty in admitting the presence of this "spine". In a private letter to me Houghton says:- "I have never been able to satisfy myself that fresh living eggs show a spine such as Leiper has described. . . . I have asked a number of men here in China, all of whom have seen hundreds of these cases, whether they have ever been able to make sure of this spine, but have not been able to find that any of them are willing to commit themselves to this spined egg. Leiper's photographs, however, are most convincing." On the other hand, in a recent article, I see that Matsurada[24] has confirmed the correctness of Leiper's observations, though he does not regard the spine as anything more than a local thickening of the shell substance.

Looss[38] also, being in possession of a piece of human liver permeated with eggs, and of other material sent to him from Japan, verified Leiper's discovery; though he takes exception to the term "spine", and hold

that it is not a true spine. By macerating his specimens in 10% Hydrochloric acid, Looss was able to free the eggs from the tissues in which they were embedded, and mount them in glycerine jelly. In addition to the "spine" Looss describes a "calotte" or cap, of varying size, marked off from the rest of the shell by a distinct line, and though he admits that it is not always perceptible, or of the same size or shape, or in the same position, he hints that this is probably in reality an operculum, for he says that in some of the eggs the cap had become partly or entirely detached "after the fashion of a lid". He refrains, however, from definitely committing himself to an opinion as to its nature on the grounds that he has not had opportunity of examining fresh eggs for comparison, "though", he says, " it is not difficult to guess what that is". Personally, in my examination of fresh specimens, I have never seen this "calotte", and Matsurada[illegible], in his recent paper, denies its presence. I am inclined to think it is a change produced in the egg by shrinkage of the shell, the result of preservation. With regard to the spine Looss says that, when present, it is always opposite the calotte, but he does not regard the spine as a "normal" character in the eggs of S. japonicum. He found that from 25-30% showed no trace of a spine, which, when present, "does not consist of the substance of the shell, but of some other special material applied to it externally, and probably forming a continuous, though extremely/

extremely thin, coat all round the egg", thus corresponding to the "spine" of some opisthorchis and clonorchis eggs. It is really a knob-like protrusion of the shell envelope, and not in any sense a true spine. In S. haematobium we have a true spine, consisting of the substance of the shell.

Ova of S. japonicum and S. haematobium compared.

S. japonicum	S. haematobium.
Large beautifully oval egg.	Elliptical egg, pointed ends.
Length, .10 x .07 mm.	.12 x .05 mm.
No true spine.	Definite true spine at posterior end.
Shell very delicate and transparent.	Shell thin and yellow.
Contains a ripe ciliated embryo, or miracidium.	Contains ripe miracidium.
Requires water of Summer temperature to hatch.	Requires water of Summer temperature to hatch.
Swims about actively by cilia.	ditto.
Has been kept alive 5 days, usually only 2 days.	May be kept 30 or 40 hours under artificial conditions.
No intermediate host has been discovered.	Experiments have failed to discover any intermediate host.

Infection of Man.

Such is the parasite, with its egg, and the free swimming miracidium which hatches from it. How does this parasite effect its entrance into man? In my first/

first paper[1], published in [illegible], and to which I have already referred, I expressed the opinion that the embryo gained admittance to the human body directly through the skin, and I still adhere to this view; indeed I am more convinced of this than ever, notwithstanding the emphatic contentions of others to the contrary. How, then, is a person who harbours this parasite a source of danger to his fellows? In a patient whose internal organs are invaded by this worm, the eggs pass out in enormous numbers in the faeces. This, of course, is readily verified by the microscope; and we find also, from microscopical study, that the addition of water is necessary to cause the eggs to hatch. If the eggs do not reach water, the miracidium will not hatch out, and the embryos will perish. But if, for example, infected faeces are deposited on swampy ground, or in any surface water, which is of summer temperature, the embryos will soon burst from their shells, and, by means of their cilia, swim actively about. My contention is that having reached water, and, under favourable conditions, hatched out, "the only way", to quote from my own article[b], "in which one can conceive of the countless swarms of free-swimming active little creatures effecting an entrance into man, is through the skin. If taken into the stomach in drinking water, either directly or in some small mollusc or other intermediary host, the activity of the gastric juice would doubtless be fatal to them." The patients who present themselves at the clinic/

clinic, afflicted by this truly awful verminous infection, are, almost invariably, fishers, boat-men, labourers from the inundated rice-fields, and others; men who are constantly in and out of the water, frequently standing in the mud for hours together, with water, it may be, up to their waists, and thus exposing, for more or less lengthened periods, a large amount of skin surface to infection.

Tsuchiya[18], in a very full account of the disease as he found it in his Japanese patients, argues for infection per os. He maintains that the infection is conveyed by drinking contaminated water. His arguments are mainly based upon the observed fact that the disease occurs for the most part among the poorest people of the country-side, especially farm labourers, who, he says, are in the habit of drinking water straight from the ponds and rivers, whereas the better classes among the population only drink water that has been boiled or filtered. Tsuchiya mentions that the disease is especially bad along the rivers Kamanashi and Fuefuki, which periodically overflow and spread infected faecal matter (deposited on their banks) into the fields. He states that there are other parts of the same province in which the parasite is not found. It is strange that he does not seem to realise that it is just those farm labourers, boat-men, etc., to whom he refers, who constantly work bare-legged in the water, while the better classes are not engaged in the same avocations, and, moreover/

moreover, go about completely clothed, and are thus protected from even accidental infection. As to the disease occurring in some localities and not in others, this is not at all to be accounted for by the fact that the inhabitants of these respective places draw their drinking-water from different sources of supply. It is true that in some localities the waters are infected, and in others not, but immunity or otherwise is not to be explained with reference to the purity or impurity of the supply of drinking-water. The presence or absence of the disease in a given place is to be accounted for by having regard to the requirements of the parasite itself, and to the occupations which are followed by the people of that district. In low-lying situations, where there is plenty of warm stagnant water, the ova of the worm will have opportunity to hatch, and the embryos to infect the fishers, paddy-field labourers, and lake-side dwellers. But in higher situations, where the soil may be sandy and drains well, where rice is not cultivated, and where there are no lakes and ponds, the parasite has no opportunity to propagate itself. Even if infected persons visit such a place, the faeces deposited in dry situations and lacking the water in which alone the ova could develop, will be comparatively harmless; they would soon dry up and the embryos perish.

In support of his theory that infection takes place via the mouth, Tsuchiya instances a place where the people all/

all drank the water from one well, and he states that as the well was uncontaminated there was no Schistosomiasis there. As regards the use of wells, however, these are certainly not likely to become infected, for the temperature of well-water is below that required by the miracidia for hatching. But it is not because the inhabitants of the place instanced by Tsuchiya all drank the uncontaminated water of a certain well that they escaped schistosomiasis, but in all probability because that place was not an endemic focus of the disease, and the conditions required by the parasite for its life and growth were lacking. This is the more likely to be so from the fact that the people of that place depended upon wells for their water supply, a circumstance which indicates that other sources of supply, such as rivers and ponds, were absent. All who have lived among Eastern peoples know that they will take their water from the nearest supply, and that they would certainly not trouble to draw water from a well if it could readily be baled from any pond or collection of water near at hand, and that quite irrespective of the quality of the water. Wells are resorted to when natural surface supplies are not sufficient, and the fact that the natives of the place to which Tsuchiya refers depended upon wells for their drinking-water, is presumptive evidence that such was the case in this instance, that it was, therefore, not a suitable habitat for the worm, and was not an endemic focus of the disease. In any case it would be necessary/

necessary to know something more of the facts of the case, especially in regard to the daily occupation of the people who lived in this place and drank this well-water, before the evidence could be considered as being of any material value.

Although in my paper previously alluded to[1], I gave it as my opinion that infection via the mouth through drinking contaminated water was a most unlikely hypothesis, as I could not believe that the delicate embryo of S. japonicum could run the gauntlet of the human gastric juice. I had not experimentally tried the effect of applying diluted Hydrochloric acid to the miracidium. I was very interested to find, therefore, that in 1910 Katsurada[15] published in German his experiments, which were designed to show (1) that the embryo of S. japonicum could not survive the gastric juice, and (2) that infection could experimentally be shown to take place through the skin. With regard to the effect of acid on the miracidia, Katsurada says that he found them very susceptible to the action of acids of different kinds. He states that a 1% solution of H Cl killed the free-swimming embryos immediately, and he concludes that it is highly improbable, if not absolutely impossible, that S. japonicum embryos could survive the passage through a healthy human stomach.

Katsurada was strongly of the opinion that the disease was conveyed through skin-contact with infected stagnant water. He dwells on the commonness of the disease/

disease in the farm-labourers, who stand for prolonged periods in the water covering the rice-fields. He mentions also that these labourers are frequently affected by an itching eruption of the exposed parts, in particular the legs, and he regards this as the result of the invasion of the human host, through the skin, of multitudes of living embryos. Personally, I have not met with this particular skin condition. Very likely it occurs only in very heavy infections, and even then is probably of a passing nature and soon forgotten (if at all noticed) by the patients.

Katsurada and Hashegawa then proceeded with certain experiments to show more certainly that infection took place through the skin, and not per os. It has already been mentioned that cats and dogs of endemic areas are also frequently affected by schistosomiasis, so that the experimenters had the great advantage of being able to use these animals for their experimental work.

The experiments took place at an infected place called Nishidai in the province of Okayama, in the month of June, 1909. The cats and dogs employed were imported from an uninfected locality of the same province. The stools of the animals were first microscopically examined to prove freedom from infection, and they were fed on carefully prepared condensed milk so that infection per os could be entirely excluded. The animal experimented upon was kept, as it were, in stocks, having a wide cangue fitted around the neck, as shown in the accompanying

accompanying illustration, the object being to effectually preclude any possibility of oral infection. The rest of the body was then immersed in the contaminated water of one of the rice fields, the head remaining free.

Experiment 1.

A female cat was put into the water for half-an-hour on three successive days, June 12 - 14. She was then brought back to the laboratory at Okayama, and carefully nourished. She gradually lost flesh from the beginning of July onwards, and by the middle of the month S. japonicum eggs could be demonstrated in the faeces. After this there was frequent vomiting, and progressive emaciation; latterly she declined to take any food and died July 20. The post-mortem examination revealed many adult male and female S. japonicum worms in the portal vein and its tributaries. Most of the male worms were about 10 mm. long, the females generally a little longer. Ova were very numerous in the liver and intestinal walls, around which granulation tissue had formed. A certain number of these eggs already showed miracidia with clear cilia.

Experiment 2.

A small puppy, a few months old, was treated in the same way as the cat. It also got thin from the beginning of July, and from the middle of the month onwards passed slimy blood-stained stools that contained an/

an extraordinary number of schistosome eggs. Vomiting supervened and complete loss of appetite, and the animal died exhausted on September 4. The post-mortem examination, held immediately after death, showed a great number of S. japonicum worms; many thousands were crowded in the portal vein and its tributaries. The worms were larger than in the case of the cat. A large number of the males reached a length of 11 - 12 mm., whereas the females measured more, one even 17 mm.

Experiment 3.

On July 17, by means of a catheter and funnel, another small dog was supplied with contaminated muddy water taken from the infected village of Iwanari, in the province of Hiroshima. After the experiment, which ensured the introduction of infected water directly into the stomach, the dog was brought back to the laboratory at Okayama. All microscopic investigation of the stools for schistosome ova were negative. The dog was killed on September 15, and the post-mortem examination failed to discover any infection by Schistosoma japonicum worms.

Experiments 1 and 2 clearly show that the embryo is capable of penetrating the skin, and that infection takes place by this route. They show also that, having gained entrance to its host, development is very rapid, the stage of the mature adult worm being reached within a month.

Experiment/

Experiment 2 upholds the contention which I had previously advanced that infection could not, and does not, take place by the ingestion of living embryos taken into the stomach in drinking-water.

The argument from Analogy.

In considering the route of infection chosen by the living embryo of S. japonicum, one naturally turns to the Egyptian species, Schistosoma haematobium. As the two species are so closely related it is not improbable that their modus operandi will be upon similar lines. Looss has successfully proved that the larvae of Ankylostom. duodenale can penetrate the skin, indeed it is now well known that that is the usual, if not the only, route of infection. It is, however, far more to the point to consider what happens in the case of the Trematodes, and especially Schist. haematobium. It is true that in the case of the trematodes we may have very elaborate histories, and more than one intermediate host may be involved in the worm's life-story. There may be four stages through which a trematode passes, namely, the miracidium, sporocyst, redia, and cercaria. The first stage is invariable spent in water; each of the other three, however, may be passed in a different host. The histories of the different trematodes, so far as they are known, are, however, very dissimilar, and all kinds of modifications exist in the life-cycle. The simplest modification of all would appear to occur in the case of the/

the Schistosomidae, in which apparently we may have no intermediate host at all, the miracidia being capable of entering directly into their definitive host, and there growing up to maturity. It is possible that certain developmental changes may occur in the miracidium before it effects its entrance into man. These, however, if they take place, are changes in the embryo itself, preparatory to its invasion of its definitive host, and does not affect the question of an intermediate host. I hope presently to refer again to this point.

Some workers in the East seem to find difficulty in believing that the miracidium of S. japonicum is capable of infecting man by entrance through the skin. It might be pointed out, however, that the usual route of entry which miracidia adopt, whether it be of intermediate or of definitive host, is via the cuticle. It is well known that, owing to the plasticity of their bodies and to their being furnished with a rostrum and with cilia, the miracidia of other trematodes succeed in penetrating the skin of various molluscs. There would appear, therefore, to be no difficulty as regards the capabilities of the embryos of S. japonicum to infect man by the skin route. The argument is also used that there must be some intermediate host. This I cannot see to be at all necessary, both from what we know of the habits of free-swimming miracidia, and from what we know of the varied and elaborate modifications which obtain in the life-cycles of the trematodes. Moreover,

to/

to turn again to the African species, S. haematobium, systematic search has so far failed to reveal any trace of an intermediate host, which, from consideration of other trematode worms, might be supposed to exist. Looss has long claimed for the Egyptian species that an intermediate host, other than man, is, in the nature of the case, a most unlikely hypothesis, and he assumes that man is himself the intermediate and definitive host in one. He argues that the miracidium enters directly into man through the skin. He excludes the possibility of entry by the mouth in drinking-water because he has shown by experiment that the embryo cannot live one minute in a solution of 1 to 1000 H Cl, nor for three minutes in a solution of 1 to 2000. As the acidity of the human stomach is said to be about .2% (2 to 1000), it does not seem possible for the miracidium to live there. The analogy of such a closely related variety as the African worm is, therefore, entirely in favour of the contention that the embryo of S. japonicum also enters directly through the skin of its definitive host, and that the assumption that there must be an intermediate host is entirely unwarranted, and highly improbable.

We come then to this, that the disease is water-borne, and that infection is conveyed through the skin. A study of the natural history of the parasite, and experimentation alike, show that water is essential to the life of the embryo. If the ova of the parasite, passed out with the excreta of its host, do not reach water/

water, no further development is possible and the miracidia-containing eggs perish. If water, for the most part stagnant, and of a suitable temperature, is reached, the miracidia hatch and enter upon the free-swimming stage of their existence. Water contaminated in this manner is highly infective both to man and the domestic animals. Hence the danger of bathing in the creeks, or wading in the ponds, rice-fields, and stagnant waters of Central China and Japan; for to allow the contact of such polluted water with the unprotected skin is to invite the invasion of an army of this insidious and invisible foe. Taking advantage of their plastic bodies and microscopic dimensions, the embryos insinuate themselves through the skin, probably along the hair follicles, and quickly effect an entrance into their unconscious and unsuspecting host.

Does the free-swimming miracidium undergo any morphological change after being liberated in the water and before penetrating the skin of its future host? When S. japonicum ova are hatched artificially in the laboratory, the miracidia may be kept alive for a day or two but no further change can be observed to take place in them. By putting infected faeces into pure tap-water at 66°F., Katsurada found that the eggs hatched out very quickly, some within fifteen minutes, others in from one to three hours. The miracidia were very active, bu they generally died in about twenty-four hours, though

some lived for forty-eight hours. Higher temperatures (103°F. and upwards), and lower temperatures (under 50°F.), were found to delay or prevent hatching. This is what we find in the laboratory, but it is quite possible that in a natural state, as in the warm open ponds and ditches, where the conditions are much more favourable to its development, the miracidium may live for longer periods, and may even undergo some morphological change. Katsurada[24] upholds this view in his article recently published in Germany. He says that the miracidia hatched from the eggs undergo a relatively simple metamorphosis by which they develop into minute larvae that swim about in the water, and by penetrating the skin invade the body of their host. This microscopic larva is said to resemble the mature worm in form - to be, indeed, as it were, a miniature representation of the adult stage. Matsuura and Yamamoto are said to have proved the presence of these larvae, still covered by cilia, in the outer skin of experimentally infected animals, and also in infected ditch-water. The measurements given are .06 or .07 mm. long, by .02 mm. broad. Miyagawa also published the discovery of a similar larva in the femoral and saphena veins of artificially infected dogs. He described the larvae as being of an elongated oval shape, .04 by .01 mm. He found them also in the skin of the infected animals.

It would appear then that the Japanese investigators consider/

consider that the skin is invaded by a very small larva, which is not the miracidium, but a minute stage of the adult form. Their work, careful and patient though it has been, requires elaboration and confirmation. For my own part, and failing direct evidence to the contrary, I am inclined to regard the "larva" as but the ciliated miracidium in an elongated form, a form it is capable of assuming, and naturally would assume, before penetrating the skin.

Having penetrated the skin, by what route do the embryos of S. japonicum reach the Portal System? This we do not know with certainty, but it would appear probable that under the dermis the young brood would be taken up by the lymphatics and passed on into the venous system. Thence to the right heart and through the lungs to the left heart, and so into the greater circulation. In the venous return from the lower half of the body the embryos would reach the portal vein system in the liver. On this point opinions are divided, but it seems the most likely and the most natural hypothesis, and in support of it, it may be mentioned that the youngest forms have not seldom been met with in the venous blood of the systemic circulation, and sometimes, though very rarely, in the arterial blood of the same. Katsurada is of the opinion that the embryos may also reach the portal vein system direct from the inferior vena cava by way of the vena hepatica.

That the embryo of S. japonicum lives in the water and/

and infects man through the skin is capable, of course, of practical demonstration. But to subject oneself or anyone else to an experiment of this kind would be unjustifiable. Animals, as we have seen, are readily infected artificially, and as for man, the experiment is in reality going on, on a tremendous scale, over large tracts of country both in China and Japan. I refer to the infection of thousands upon thousands of farmers, lake-side dwellers, fishermen and boatmen, living in these parts, who, by constantly wading about in polluted water in pursuit of their daily avocations, become very heavily infected by this noisome parasite, and the prey of a loathsome and deadly malady.

From this it will be clear that the disease is occupational in origin. It is those who work in the water who get infected; and those who work in the water are, for the most part, the men and boys. It is on them that the duties of cultivating the rice-fields, and other farm-work, devolve. They manage the boats and do all the fishing. Consequently it is in the male sex that we find the disease, and not among the women and girls. The latter, in China at least, invariably go about well clothed. Their feet are crushed and deformed from infancy, owing to the pernicious custom of foot-binding, and not the feet only but also the legs are always kept well bandaged and clothed. They are thus protected from infection even if they did occasionally come in contact with contaminated water,

but,/

but, as a matter of fact, the women in Central China are not equal to, and do not participate in, field-work, where such involves heavy wading, as in the rice-fields. This kind of work is left to the men and boys, the women merely helping in such dry occupations as sunning and sifting the grain. I have never seen a case of S. japonicum infection in a female, and Houghton, who has seen many hundreds of cases of the disease, writes me that he only once saw a case in a woman. Thomson, of Hankow, also wrote me that he had never seen a female case, and he remarks that all his patients have been very positive in asserting that women do not contract the disease. For the reasons given, infection in women in China must be rare, though, of course, it is perfectly possible. A woman may get into contact with contaminated water in other ways, as, for example, by bending down and washing at the edge of a pool, or dipping the hands in the water while sitting in a boat. In Japan, where foot-binding is not in vogue, the women frequently work in the rice fields, standing bare-legged in the water, and such women, of course, get infected and suffer from the disease in the same way as the men.

I have emphasised this point because it furnishes additional proof that the disease is of occupational and not of dietetic origin. If infection took place per os by the drinking of contaminated water, then women would suffer in the same manner and much to the same extent as the men.

mon, for the inhabitants all draw their drinking-water from the same sources. The fact that nearly all the males (except the young children) of a certain place become infected, and practically all the females escape; that the boys and men of a household become diseased, while the girls and women remain free - surely shows that infection is not carried by the drinking-water which is in the common use of all. It goes to prove the point for which I have contended since first studying the disease, that, though infection is derived from the water, it is not through the mouth that it comes but through the skin, and thus it is that it occurs almost exclusively in the male sex, i.e. those who, from the nature of their occupations, are in the habit of exposing their bare skins to infection.

If we turn again to the closely allied affection, bilharziasis, where also, according to Looss, we have the miracidium directly infecting man through the skin, we naturally find very much the same state of things, viz., those who expose themselves, whether men or women, become infected. We read that in Egypt, among the poorest classes, both men and women work together bare-legged in the muddy fields, and both sexes suffer equally from bilharziasis. In better classes, where only the men work outside, these only become infected, and the women escape. Still higher in the social scale, the men who do not work in the fields, but find other means of livelihood, as clerks in offices and such-like, do not contract/

contract the disease. Yet the drinking-water is the same for all three classes, i.e. unfiltered water, direct from the Nile.

It is only necessary, therefore, that liquid mud or water contaminated by the living embryos of S. japonicum should remain for a short time in contact with the skin for infection to take place. In the country-towns and villages of the endemic areas, both in China and Japan, the ponds and rice-fields are being constantly fouled by the inhabitants, who not only use human excrement for fertilizing purposes, scattering the same freely over the surface of the ground, but who also have the objectionable habit of defaecating promiscuously in the open, wherever they may find it convenient to do so, whether it be in garden, pond, or rice-field. The eggs of the parasite, passing out in enormous numbers in the stools of those infected, will quickly hatch out on reaching the water or warm liquid mud of the "paddy-fields", and, as the embryo will live for a couple of days or longer in this water, there exists ample opportunity for the unsuspecting coolie, who, in pursuit of his daily avocation comes wading in pond or rice-field, to be come infected.

As we have already stated, nothing is definitely known of what happens to the invading embryo from the time it enters until the time when adult forms are found in the portal and mesenteric veins. The miracidium presumably enters the skin along the hair follicles, effects/

effects entrance into the lymphatics, and then, carried first by the lymph and then by the blood stream, will reach those vascular structures for which they have a special predilection, notably the Portal vein and its branches. It is in these regions in the liver that the parasite makes its home and rapidly grows to maturity. It is here that the sexes meet, and, travelling in pairs along the portal vein tributaries, produce a prodigious and continuous stream of ova, which, by their mechanical blocking of important channels and organs, result in such sickness and suffering for their host.

ETIOLOGY.

After the foregoing it will not be necessary to say much concerning the etiological factors predisposing to this disease. The first and most important of these is Residence in an endemic area. I have already emphasised the endemic nature of the disease: naturally those who live in the infected areas are those most liable to contract the trouble. The disease is not readily imported to other places where the conditions are not favourable to the development of the ovum, hence those who live outside the foci of the disease may be regarded as comparatively safe.

Age. The disease, as one would expect, is unknown in infants, but may be found in males at any age from, say, 5 or 6 to 60; that is from the time that small boys are able to run about in the water, to the time when adults/

adults cease to participate in the active work of making a living. Children are not usually infected before 7 or 8. In a series of forty cases which Houghton reported[6], the youngest was 16, and the eldest 54. Doubtless these are the ages between which infection usually occurs, as they represent the working period of life, but this number of cases is small, and there is, of course, no age limit of infection.

Sex. In China it is the male sex, almost exclusively, that is affected. The reason for this has already been given. The case is rather different in Japan, where the women's feet are not bound, and where they frequently work in the flooded rice-fields along with the men. Sex, in itself, is not, of course, a determining cause. It is a matter of exposure to infection, and those will contract the disease who, whatever their age or sex may be, expose their naked skin to the contact of the contaminated waters in the creeks and lakes, in the ponds and paddy-fields, of infected localities.

Occupation. This has already been fully dealt with. The disease occurs almost entirely among the farm-labourers and rice-growers, fishermen, boatmen, and lake-side dwellers whose occupation necessitates constant wading in the water. Occasionally an odd case will be found in others who do not belong to this class as, for example, in a small shop-keeper; but if so, inquiry into his history will reveal the fact that he formerly was/

was engaged in farming or fishing or kindred occupation. Or it may be that though the patient is engaged in some city calling and has never been employed in these country avocations, yet careful investigation will elicit the information that he has indulged in bathing (it may be only very occasionally) in the ponds or creeks of the neighbourhood.

Climate and Season. Something has already been said regarding the climate which is essential to the parasite's life and development. The low-lying, hot, steamy plains and muddy levels of the Yang-tse Valley, annually flooded by the over-flow of the great river, form the breeding-grounds par excellence for the parasite. The conditions of high temperature and abundance of water which are indispensible to the parasite's development, are here ideally fulfilled. Unfortunately these also are the requirements for the successful cultivation of the rice-crops, and thus it is that when, in the warm Summer months from May to August, the peasants are busy planting out their rice or attending to their other duties in the fields, the miracidium is most active as an infective agent. The combination of warmth and moisture are essential, and the disease is thus limited to those tropical climates where these conditions are fulfilled.

Races. No race is exempt from the disease. All who expose themselves are liable to contract it. British and/

and American officers and men from the gun-boats stationed up the Yang-tse, who go ashore shooting, and wade in the water after duck and snipe, not infrequently get infected.

PATHOLOGY.

The pathological changes which we find post-mortem in cases which have died from S. japonicum infection are many and profound. In some cases they are more marked than in others, varying according to the degree and the duration of the infection in the particular case under investigation. The longer a case has lasted, or the heavier the infection, the more marked and severe will be the resulting lesions.

In order to appreciate the reason for the morbid changes which take place in the abdominal viscera in this affection, it is necessary to have some idea of the movements and behaviour of the parasite itself. Having penetrated the skin, the embryos, as we have seen, gain the blood stream, and are carried to the venous capillary network of the liver. Here the young forms congregate and grow rapidly; indeed, the liver may be said to constitute the great nursery of the young parasites.

As the worms mature, of necessity they must leave the blood vessels of small calibre and migrate into the larger portal vein system, where they will have room to grow. This movement, although against the blood-stream, is probably accomplished by the parasites' wriggling movements/

movements, and by the use of their suckers, by means of which they cling to the vessel walls. In the larger vessels the worms reach the adult stage, and as they become mature the sexes unite, the female worm enfolded in the gynecophoric canal of the male. In this fashion the paired couples migrate along the portal vein, and up its great tributaries, until they reach the smaller radicles of the portal system, notably the veins of the mesentery and of the intestines, many of which they block up with their bodies. Having reached these situations, ova are deposited.

It will be noted that the worms make their way against the venous blood-stream, and that the anterior or head-end of the parasites will necessarily be the distal end from the liver. Now, as the coupled worms, attached by their suckers, block the vessels in many cases, and as the eggs are eliminated through the sexual pore at the anterior part of the female, it will be seen that the ova are crammed in between the parasites themselves and the vessel walls. Also the venous blood-stream coming down against the worms prevents the eggs from escaping distally; on the contrary the blood endeavours to carry them past the obstruction. Owing to the enormous number of the eggs deposited, the pressure eventually becomes so great that the walls of the vessels rupture, and thus the ova are forced into the surrounding connective tissue, intestinal or mesenteric. In the case of the intestinal

vessels/

vessels the mucous and submucous tissue will be involved, and the mucosa is liable to break down in patches, because, owing to the blood-stasis, impaired nutrition, and lowered vitality, it will be attacked by pathogenic bacteria in the bowel, and local ulceration will result. It is in this way that the eggs pass into the lumen of the intestines, and so out in the stools.

The bodies of the parasites are well adapted for wedging themselves into the smaller veins, and as the male can firmly embrace the female in the gynecophoric canal, and as both are provided with suckers, they are easily capable of holding their own against the blood current. The parasites and their eggs, as we have seen, thus cause obstruction and venous congestion in the bowel walls and mesentery. After rupture of the vessels, from the pressure caused by the ever-increasing number of eggs, there will, of course, be haemorrhage, and the ova will be distributed in the surrounding tissues, notably in the intestinal walls and mesentery. In some post-mortem examinations which Tsuchiya[14] performed on cats, he found coupled parasites in many small veins in the bowels and mesentery; he found also marked capillary dilatations in the submucosa, with agglomerations of newly-deposited eggs, and fresh haemorrhages in the neighbourhood.

We have now to consider what becomes of the eggs deposited in the situations already indicated.

(a) Eggs escaping into mucosa and submucosa of intestinal/

intestinal wall produce irritation and active inflammatory changes. We get connective tissue proliferation and marked thickening of the gut. Ultimately ulceration of the mucous membrane takes place. It is as a result of this that we get the dysenteric symptoms which constitute such a characteristic feature of this disease. It is in this way also that the ova gain access to the interior of the bowel, and so pass out in countless numbers in the stools.

(b) Many of the eggs deposited in the loose submucous tissue of the intestinal wall will get taken up by the lacteals and be passed on to the mesenteric glands. Likewise, through rupture of the smaller mesenteric veins, eggs will be extravasated between the layers of the mesentery, and also be carried by the lymph stream to the mesenteric lymphatic glands.

(c) Where the worms are not fitted tightly in the veins, but clinging to the walls of the larger vessels, the eggs as they escape from the female, will be carried by the venous blood stream past the bodies of the worms, and will be conveyed along the portal blood until they reach the terminal ramifications of the portal vein in the liver. It is probable that these vessels have already become narrowed by endophlebitis, the result of irritation caused by the young forms of the parasite when, in the first place, these took up their abode in the liver. They will thus the more readily become occluded/

occluded by the myriads of ova brought down by the portal blood-stream. The irritating presence of these eggs, crowded up as they are in such enormous numbers, results in profound pathological changes in the liver; and the blood stasis which they cause leads to signs and symptoms which we are accustomed to associate with acute portal obstruction.

By piecing the evidence together it seems to me that the foregoing description fairly accurately depicts what actually happens from the time that the embryo penetrates the skin until the adult forms are found occupying the venous radicles of the portal vein. It is only by having a clear conception of the movements of the worm, and of the positions which it takes up in the veins of the abdominal viscera, that we are enabled to understand the meaning of the gross lesions which we find on post-mortem examination of these cases.

From all that has been said it will be seen that the most important pathological changes should be looked for in the liver, in the intestinal walls, and in the mesenteric glands. Undoubtedly it is the liver and the large intestine which bear the brunt of the disease. Clinical examination reveals in many cases a marked thickening of the large gut, as well as enlargement of both the liver and the spleen. The swelling, in the case of the spleen, is, I believe, an inflammatory condition due to the toxin elaborated by the worm and circulating/

circulating in the blood. In the case of the liver there is seen during life an obvious obstruction in this organ. I first attributed this portal stasis to the irritating presence of the parasite itself, setting up a peri-vascular cirrhosis, with consequent constriction of the vessels. It was difficult to say with certainty what was the immediate cause of the portal block, as post-mortem examinations are most difficult to obtain in China, the native prejudice to any such proceeding being almost insurmountable. Later I realised that the obstruction to the portal circulation was caused not so much by the parasite itself as by its ova. The settling of ova in the liver at first causes hyperaemia, and then interlobular cirrhosis, manifesting itself clinically by enlargement and tenderness of the organ. In the course of time a coarser cirrhosis sets in, with contraction of the fibrous tissue, and then we get shrinkage of the organ, with, of course, very extreme ascites.

To obtain more exact knowledge of the pathology it was essential that post-mortem examinations should be made, and I am glad to say that, under exceptional circumstances, my friend Dr. Thomson of Hankow was enabled to perform an autopsy in the case of a youth who had died of the disease in his hospital at Hankow. Writing of this case in a private letter to me, Thomson states that his patient was a garden-coolie, aged 22. His complaint was of fever, dysenteric symptoms and great weakness. He stated that five months previously his/

his abdomen had begun to swell. "He was carried to the hospital in a dying condition, extremely emaciated. All but the abdomen, which was distended with fluid to such a degree that the patient could not support its weight. He was in fact all abdomen with thin emaciated trunk and extremities attached. Next morning he died before anything was done for him." The liquid stools, which had been examined microscopically on his arrival, were found full of S. japonicum ova.

In order to examine the ascitic fluid, some of it after death was withdrawn with an aspirating needle from the abdominal cavity. It was found to be thick and chylous, unlike the clear ascitic fluid usually withdrawn in such cases. The nature of this fluid was suggestive of Filariasis, but Dr. Thomson could discover no filaria in the blood from the organs, in the ascitic fluid itself, or in the sections which he afterwards prepared. He was of the opinion that the condition could be accounted for "by pressure upon lacteals or thoracic duct by the enlarged peritoneal glands".

"After opening the abdomen" Dr. Thomson writes, "and getting away all the fluid (there were about 30 pints present), the most striking feature was its extreme emptiness, the bowels, liver and spleen having all been compressed and pushed upwards under the ribs, or back along the spine.

"The large intestine was found to be very much thickened, very much matted together with the ileum near the/

the caecum, and, in this region, with enlarged lymphatic glands. The greatest thickening was found to be at the caecum and rectum and sigmoid, but thickening was marked throughout its length. There was some thickening of the small intestine but not very much.

"The peritoneal lymphatic glands were all very much enlarged and matted together, especially near the caecum, where they formed quite a tumour.

"The Spleen was not abnormal, beyond being shrunken and wasted like the rest of the body.

"The Liver perhaps was the most peculiar feature; it was shrunken, hard, and bossed all over, and pushed away up under the ribs. On section it looked like a German sausage, that is, it was dotted all over with white areas varying in size from a pin's head to ten or twenty-cent pieces, (from a sixpenny piece to a shilling). The liver substance itself was of a slaty purple colour, due probably to numerous minute specks of cirrhosis which were afterwards seen well under the microscope. The hepatic veins were widely open, but the portal veins were everywhere surrounded by dense cirrhotic tissue, and at the hilum of the liver this tissue was specially dense and thickened.

"Juice expressed from the peritoneal glands was milky in appearance and teemed with schistosoma ova, most of which showed the embryo clearly and in active motion; in others the embryo was not quite fully developed/

developed, and in others degenerative changes had evidently taken place. From gland juice I was able to hatch out embryos and watch them under more favourable conditions than usually obtain in faeces.

"I was unable to find ulceration of the mucous membrane of the colon as described by Catto, but instead I found everywhere warty-like excrescences, rather hard and fibrous to the touch.

"Microscopical examination. Sections of the bowel showed ova teeming in the mucous coat covering the warty growths; the fibrous layers were much thickened. The Glands were simply packed with ova, many having undergone calcareous degeneration. With regard to the white areas visible to the naked eye in the Liver, these consisted of dense fibrous tissue containing numerous ova. Between the lobules were numerous small areas of fibrous tissue containing ova, giving one the impression of a portal vein terminal plugged with ova and surrounded by fibrous tissue. Nowhere in my sections did I come across an adult worm. Altogether in the liver, glands and intestines there must have been countless millions of ova; but in the intestines much fewer than in the former two organs."

I have quoted freely from Dr. Thomson's letter for I think he has very ably summed up in a general manner the chief pathological changes which we find in this affection; and these are exactly the changes we should have expected from a consideration of the movements of the

the parasite, its location in the portal vein radicles, and its egg-laying propensities.

Dr. Thomson was also kind enough to give me a small cube of the liver substance taken from his post-mortem case. This I sent home from China to Dr. F. M. Sandwith, who had it sectioned by Professor S. G. Shattock. Shattock reported on it as follows:-

"The microscopic sections show foci of small-celled infiltration in the interlobular connective tissue, formed around small groups of the ova of the parasite. In many cases the ova are dead, and their chitinous capsule collapsed. The proper hepatic tissue is uninvolved. In the case of the larger portal canals the infiltration is more diffuse, but here the same minute knots of more acute formation occur, the centre of each of which is constituted by a group of ova."

My letter, together with the specimens, were brought by Sandwith before a meeting of the Society of Tropical Medicine and Hygiene, and afterwards fully reported in the Transactions of the Society for June 1910. I have pleasure in submitting, with this Thesis, some of the sections cut and stained by Professor Shattock from the sample of liver which I sent home, and in these the changes described by him will be clearly seen.

It appears very evident, from all that has been said, that the disease must be regarded primarily as a portal vein infection; though apparently there are still some who think of the parasite as inhabiting the smaller arteries.

arteries of the abdominal and pelvic viscera. And the worms undoubtedly occupy the venous radicles of the portal system, and the pathology is, to a large extent, due to the mechanical obstruction produced by the ova, which, issuing from the parents in a continuous stream, are carried upwards by the blood current to lodge themselves finally in the small interlobular capillaries of the liver, where they excite cirrhotic changes. As more and more terminals become blocked, and as the cirrhotic changes advance, the stasis becomes so profound as to manifest itself by extreme degrees of ascites, and other clinical phenomena, which lead up to a fatal issue.

"It is difficult" Thomson remarks, "to explain gland and intestinal blocking, unless one assumed that certain adults must be lying in the tissues shedding ova into lymphatic channels, or, in the case of the intestine, into arterial radicles. It would be interesting to find out the exact location of the adults. A location in the vein radicles would explain the liver and portal vein phenomena, but not the glands or discharge of ova into the intestine; a location in arteries would explain ova in the intestine, but not in the liver or glands; a location in the tissues would explain the presence of ova in the glands, but not necessarily in the liver or intestine. . ... The fact that ova are so numerous in the lymphatic glands would lead one to suppose that certain of the adult worms must be lying in the tissues and not in the veins." It will be seen from this that the/

the distribution of ova at one and the same time in liver, lymphatic glands, and intestine, was a mystery to Thomson, as it has been to all who have studied this extraordinary disease. This fact has made the location of the parent worms difficult and puzzling. Thomson evidently inclines in favour of the view that the adult worms are situated in the venous radicles of the portal system, but on that supposition he cannot account for the presence of ova in the lymphatic glands of the mesentery and in the intestine (both in the intestinal wall and in the lumen of the gut). He thinks that the presence of ova in the glands indicates that some of the worms must be located "in the tissues and not in the veins". I have already stated my view in regard to this matter. The adult worms live in the branches of the portal vein system, such as the mesenteric veins. In these larger branches, where there is plenty of room for the parasites, their eggs are swept past them by the blood current, to lodge in the terminal capillaries in the liver. The fact that ova are found also in the intestinal walls and in the lymphatic glands does not, in my opinion, militate against this view. It only means that some of the worms have travelled far enough up the veins to reach the venous radicles near and in the intestinal walls, here to plug the small vessels and deposit their ova in the manner I have indicated. The vessels, subjected to unusual pressure, rupture, the eggs are infiltrated through

mucous/

mucous and submucous tissue, ulceration occurs, and ova are shed into the bowel. Many others, breaking through the small vessels and deposited under the mucosa of the bowel or between the layers of the mesentery, are taken up by the lacteals and lymphatics and so conveyed to the mesenteric lymphatic glands. This view is in accordance with all that we find in this disease, being borne out both by the clinical features and by the pathological findings. It explains the presence of dysentery and ascites during life, and accounts for the changes in the liver, mesenteric glands, and intestine, which we discover after death.

In order to investigate the pathology of Asiatic Schistosomiasis in more detail it is necessary to study the reports of post-mortem examinations that have been published by those who have made a special study of the disease, and though this may lead to some repetition it will serve to corroborate the findings and impress the pathological picture presented by this morbid condition.

In Catto's case[2], to which reference has already been made, the right lobe of the liver was found during life to extend two fingers' breadth below the costal margin. The left lobe was a hand's breadth below the sternum and its percussion dullness merged into the splenic. The spleen was palpable one inch from the iliac crest. At the necropsy Catto noticed that the appearance of the peritoneum suggested repeated attacks of/

of peritonitis. The mesenteric tissues were all thickened. The mesenteric and prevertebral glands were enlarged. The liver was uniformly enlarged, and its surfaces were markedly nodular, the whole having the appearance of a coarse cirrhosis. "The colon", Catto says, "was much thickened throughout. The mucous membrane was swollen, hyperaemic and friable, presenting numerous small circular superficial erosions and patches of necrosis. The outer coats were very tough, almost cartilaginous, and showed no tendency to ulcerate. The rectum was three-quarters of an inch thick all round, and was adherent to the bladder. It nearly filled the true pelvis. Where adhesions had formed the bladder wall was thickened, but elsewhere it was healthy, and nowhere was the vesical mucous membrane diseased. The sigmoid was uniformly thickened; in tracing the bowel upwards the thickening became less marked and more patchy. The coats of the caecum and appendix vermiformis were uniformly hypertrophied, the mucosa presenting small patches of ulceration and necrosis. The appendix was provided with a mesentery, and a distended lymphatic could be recognised running along its free surface. The liver and bowel cut gritty on section. The lower end of the ileum was thickened in patches and the mucosa congested over corresponding areas. The enlarged spleen was pigmented. The stomach, pancreas, supra-renals, kidneys, heart and lungs showed no sign of coarse disease."

In/

In sections of the meso-colon Catto subsequently found adult worms in the smaller mesenteric blood vessels. He was not able to determine, in his spirit preparations, the nature of the vessels in which the parasites lay, whether they were arteries or veins. The worms were found at the bifurcations of the smaller mesenteric vessels, partially or completely occluding them.

Histopathology. Microscopical examination of the tissues show that where ova accumulate they provoke a small-celled infiltration, and this gives place later to an abundant proliferation of connective tissue. In Catto's case the rectum and appendix were severely affected, the distended lymphatic vessel in the mesentery of the appendix being choked with ova.

In the intestine, from caecum to anus, Catto found the ova to occupy roughly "two concentric layers, the one subperitoneal, where the ova are comparatively scarce, the other in the submucous coat, where they are innumerable, in some cases densely packed." Ova were also found plentifully in the mucosa, especially in the necrotic areas and ulcerated patches where they were found in process of extrusion. Ova were only found in small numbers, and scattered, in the small intestine.

In the liver ova were numerous, embedded in the hypertrophied fibrous tissue. Pigment was present both in/

in the liver and bowel.

In the mesentery and enlarged mesenteric glands were many eggs. They were also found in the outer wall of the gall-bladder, in the pancreas, pylorus, and duodenum.

As early as January 1906, Woolley[6] reported finding the eggs of Schistosoma Japonicum in making a histological study of the organs of a native Filipino, who had died suddenly of a terminal bacterial infection in the course of intestinal amoebiasis and uncinariasis. As this man had not been out of the Islands, we thus obtained evidence of the existence of Asiatic Schistosomiasis in the Philippines. Microscopic investigation showed that "the mucous membrane of the large intestine was atrophied and, in areas, eroded. The submucosa was thickened and oedematous. The muscular layers presented but little change. The ova (verified by Shiga and Stiles) occurred chiefly in fibroid tissue in the submucosa, where they were innumerable and surrounded by round-celled infiltration". Eggs were also found in the liver, and a few in the lungs, and wherever they were present they were surrounded by small-cell infiltration and fibrosis.

Matsurada[1], who studied the pathology of the affection very carefully, states that the mature worms are to be found in the portal system and its tributary branches, especially in the mesenteric veins, both in man/

man and in cats. He says the eggs appear as emboli in different organs, but particularly in the liver, where they set up inflammatory changes and proliferation of the connective tissue. Later the organ shrinks and becomes cirrhotic, the surface becoming rough and unevenly granulated. The liver changes result in marked portal obstruction.

In the intestine the eggs are found for the most part in the mucosa and submucosa, especially in the large intestine. The presence of the eggs here again causes inflammation of the tissues, resulting in destruction and ulceration, and also in connective tissue proliferation so that often small fibrous growths form on the lining membrane.

Although the vast majority of the eggs carried back by the blood stream lodge in the liver, some apparently succeed in passing through the capillary network of that organ, and are thus conveyed to other parts of the body; and nearly all the organs may be invaded, although the eggs found in distant parts may be very few indeed. Thus we may find ova acting as emboli in the kidneys, lungs, or even in the brain. A case of this kind was reported by Yamagiwa in 1890, where the case exhibited symptoms of Jacksonian epilepsy, and where ova were subsequently found in the brain-cortex. The eggs were at the time taken to be those of the lung fluke, Paragonimus westermanii, but, according to Katsurada, Yamagiwa/

Yamagiwa now assumes an error in his earlier diagnosis, and is convinced the eggs were in reality those of S. japonicum. Katsurada emphasises the fact, which can be endorsed by all who have had to do with this disease, that the parasite does not cause any bladder troubles whatsoever. In no case have I ever heard of bladder symptoms, thus showing a marked difference from S. haematobium. The mucous membrane of the bladder is always found in a healthy condition.

In August 1908 Tsuchiya[14] published his observations on several autopsies which he made in the Yamanashi Hospital in Japan. His findings may be briefly recorded as follows:-

Case 1. Farmer's wife, 29 years old. Brought to the hospital when the disease was far advanced. There were present enlarged spleen, ascites, and oedema of the lower limbs. Dyspnoea was severe. In hospital weakness increased, the pulse became small and quick, and the patient died in collapse.

Post-mortem. Body emaciated. On opening the abdominal cavity about four and a half litres of a yellowish fluid poured out. The great omentum was found adherent on the left side with the abdominal wall, and on the right side with the under surface of the liver. The peritoneum was somewhat thickened, but smooth. The summit of the diaphragm coincided with the third intercostal space on the left, and with the third rib/

rib on the right.

Liver. Size 26 x 15 x 5 cm. Weight 605 grammes. Colour brownish-yellow. The surface was studded by hemi-spherical nodules, "about the size of the end of a thumb". These nodules were separated by deep wrinkles, from which strong strands of fibrous tissue radiated inwards. The consistence of the liver was hard, and the capsule much thickened. The cut section had a brownish-red colour.

The inner walls of the trunk of the portal veins, and of the mesenteric veins, were much thickened in certain places and the surface roughened from endophlebitis. Careful examination of the portal vein, beginning with the trunk and going into the branches in the liver, revealed parasites. Three couples were removed from the coagulated blood in a large branch of the portal vein in the left lobe.

Microscopic examination showed that the small portal vein branches were occluded, their place being taken by connective tissue with deposit of eggs. The relationship between eggs and vessels could not readily be made out, and only in a few preparations could it be seen that the eggs had been entombed in the small branches of the portal vein. The eggs varied in size and form - roundish, elliptical, oval, irregular - according to their stage of development and the pressure exercised in their neighbourhood.

The liver cells showed irregular arrangement of the

rows/

rows caused by the pressure of proliferated fibrous tissue, while the cells themselves had suffered more or less from atrophy.

In the blood taken from the portal vein there was present in small quantity a brownish-yellow pigment. This granular pigment was also found in the interlobular capillary vessels.

Mesenteric lymph glands. Some of these showed no chang superficially, but on others protuberances were visible. The cut section was reddish-grey and showed brownish spots. Microscopically, eggs were found in the glands. In the brownish spots numerous eggs were found, some isolated, some forming clusters, with round-celled infiltration and proliferation of the connective tissue round about. In some instances the eggs had caused such changes that it was only possible to tell that a lymph gland had existed in that situation from the recognition of remnants of gland tissue.

The Intestine. The serous surface of the small intestine showed no change, and the mucous membrane was normal. But in the submucosa of the ileum there were many tubercles of the size of a grain of rice. In these eggs were found, with connective tissue round about.

The vermiform appendix was of normal appearance except for the presence of many hard brown tubercles, the size of a millet seed, at the root. The mucous membrane was roughened by innumerable brownish-grey tubercles of the size of a pin's head. Microscopically it could be seen that /

that the mucosa was completely degenerated from the presence of ova. Many ova were also found in submucosa and subserosa with round-celled infiltration in the vicinity, and connective tissue proliferation. Not nearly so many eggs were found in the muscular layer and in the serous membrane. At the numerous places where tubercles had formed, the mucous, submucous, and muscular layers had entirely gone, their place being taken by the crowds of eggs and connective tissue. The appearances met with in the large intestine resembled those found in other parts of the gut, only the changes were further advanced. The glandular elements in the degenerated mucous membrane were destroyed by accumulations of ova. The submucous layer was much thickened in many places and its tubercles showed two things - round-celled infiltration with few eggs, and proliferated connective tissue with many eggs. The small veins in the submucosa were enlarged and filled with blood; the lymphatics also were considerably dilated in places.

The heart and pericardium were normal.

Microscopical examination of the lungs revealed isolated eggs. Ova were occasionally found in groups, and around these the connective tissue had proliferated. There were also pleuritic tubercles, in which many ova were found and the usual tissue changes round about.

Sections taken from the spleen failed to reveal the presence of eggs. It is noteworthy that Tsuchiya never found

found eggs in the spleen.

The kidneys showed parenchymatous inflammation but there was nothing further to be found. No eggs were discovered microscopically.

The genital organs and bladder were normal.

No changes were found in the brain.

Case 2. Farmer, [illegible] years of age. Patient stated that he had enjoyed good health from childhood until the illness started. Symptoms of disease commenced in August 190[illegible]; no appetite, vomiting, and such severe dyspepsia that weakness and emaciation supervened, while the abdomen began to swell. In October diarrhoea became pronounced. It was at the end of June 190[illegible] that patient was taken to the Yamanashi hospital.

On admission patient was found to be a badly nourished man of average height. Skin of a peculiar dirty-white. Conjunctiva and lips very anaemic. The lungs were compressed upwards by the abdominal distension, but otherwise lungs and heart seemed normal on percussion and auscultation. The abdomen was filled with fluid and very tender on pressure everywhere. The liver was felt to be hard and tuberosities could be palpated on its surface. The spleen was not palpable. There was slight fever, the temperature ranging from 97°F. to 101.5°F. Diarrhoea was marked and persistent, and on it large doses of opium and bismuth had no effect whatever.

On/

On July 8th, in order to help the venous return, the Talma operation was performed, after which fever and diarrhoea decreased, but extreme weakness supervened, and on August 23rd the patient died in a state of collapse.

Post-mortem. Examination of the body showed extreme atrophy of fat and muscles. No jaundice. Slight oedema of lower part of thighs. On opening the abdomen about four litres of a yellowish fluid escaped. The great omentum was rolled upwards and adherent to the abdominal wall. The parietal peritoneum was smooth, but the visceral peritoneum was shiny, moist and oedematous, and on careful examination many small tubercles could be recognised.

The liver was pressed up towards the back, it was of a brownish-grey colour and measured 26 x 15½ x 5 cm. The surface was bossed and uneven due to the formation of fibrous tissue nodules. The cut section was smooth and showed a reticulate formation of fibrous tissue around portal vein branches.

Microscopically eggs were found in the interlobular capillary vessels, and also a brownish-green granular pigment. The relationship between the eggs and the portal vein branches could be well demonstrated in this case, for both eggs and pigment lay free within the vessels. In some cases complete obstruction of the veins could be seen to have taken place.

Portal system. In the trunk of the portal vein and

traced/

traced back to the beginning of the mesenteric veins innumerable parasites were found. Tsuchiya states that they could clearly be seen from the outside, through the transparent walls of the vessels. The parasites were numerous in the ileo-colic veins and the superior haemorrhoidal vein, fewer were found in the veins of the stomach and the intestinal wall. The lumina of the portal veins were a little dilated, the intima always being smooth.

The mesenteric lymph glands were much swollen and their consistence hard. Eggs were found in nearly all the glands.

The Intestine. A number of the veins of the small intestine were filled with parasites. The mucous membrane was covered with much mucus, and it was greatly swollen and injected. The submucosa was thickened and showed a congested condition of the dilated blood vessels, with deposits of ova, which deposits were also present among the muscular fibres, resulting in the disarrangement or destruction of the latter. Eggs were also present in the subserosa, causing proliferation of tissue in their neighbourhood. In many places the deposit of eggs seemed to be recent as the tissue reaction was not marked.

The appendix was entirely normal.

In the large intestine the mucous membrane was oedematous, and in the caecum, ascending and transverse colon it showed/

showed dirty reddish-brown spots, which, on closer examination, proved to be many points of haemorrhage. Eggs were found in the veins. Small brownish-grey tubercles were also to be seen and felt in the submucosa. The dilatation and engorgement of the veins of the submucosa, and the haemorrhages therefrom, had originated from obstruction caused by parasites. Round-celled infiltration was frequently to be found in the vicinity of settlements of eggs, as in the small intestine, and also the greenish-brown pigment. Tsuchiya says - "From one of the mesenteric veins, the walls of which were normal, I made several transverse sections, and found that the veins of the mesentery were almost entirely filled with parasites". The spleen was enlarged and soft. Veins dilated, tunica intima smooth. No parasites or eggs were discovered. The stomach. In the coronary and gastro-epiploic veins and their branches many parasites had entered. The lymph gland in the lesser curvature was enlarged, and in it many eggs were found microscopically. In the mucous membrane beyond the pylorus a small erosion existed. The serous layer over this erosion was thickened and presented tubercles of the size of a pin's head. The microscope showed destruction of the mucosa at the site of the erosion, and at the periphery there was destruction of gland tissue with accumulations of eggs. The submucosa and serosa showed marked proliferation of connective tissue and injection of the blood vessels. The tubercles on the serous surface presented the same appearances/

appearances as those in the intestine of Case 1.

The other organs of the body, though fully reported on by Tsuchiya, presented nothing worthy of special note.

Case 3. Country-woman, 27 years old. In August 1903 the patient became ill with fever, rigors, headache, general dullness and giddiness, and dyspnoea on any exertion. She had also diarrhoea with tenesmus, and the abdomen began to swell. Anaemia supervened, and the spleen enlarged and became palpable. The ascites increased, and this was followed by oedema of the legs. Haematemesis occurred. Though the appetite was maintained, emaciation progressed. In August 1904 the patient was removed to a hospital in Tokio.

State on admission. Small, anaemic woman. Pulse, small and rapid. Marked ascites, but abdominal veins only moderately distended. Oedema of the legs. Some fever present. Thoracic organs compressed upwards. Respiration of a whistling character. Systolic murmur heard at apex of heart. Diarrhoea was a troublesome feature, and on examination of the stools the eggs of S. japonicus were found. The hard spleen was easily palpable. With regard to the liver, this organ could only be palpated after tapping the abdomen. The surface was then found to be hard and uneven, with a sharp serrated edge.

Progress. The abdomen was tapped on August 27th, and this was repeated at intervals till March 28th, 1905,

in/

in all 19 times.

On September 9th, following sensation of fullness in the epigastrium, the patient vomited blood twice, the total amount being 600 c.c., and a large amount of blood appeared in the stools for the next two or three days. Haematemesis occurred on several occasions after this, and the patient became extremely anaemic; the symptoms became aggravated, and she could not leave her bed. The patient returned home on March 28th, 1908, but on May 29th she had to be removed to Yamanashi hospital, where tapping was required every five or six days. The Talma operation was performed on July 6th, after which ascites became less troublesome, but the patient gradually got weaker and died from exhaustion. Paracentesis abdominis was performed, in all, 48 times.

Post-mortem. On opening the abdomen it was found that the great omentum, as in the other cases, was rolled upwards and adherent to the abdominal wall. The spleen was adherent to the diaphragm. The height of the diaphragm corresponded, on the right side, with the fourth rib, and on the left side with the third intercostal space, so greatly were the thoracic organs compressed. The mesentery was thickened by the deposit of fat, and the mesenteric glands were obscured by fat, but could easily be felt.

The liver measured 22 x 14½ x 6½ cm. The outer surface of the left lobe was tuberculated. Capsule pale, thickened, and wrinkled. The cut section showed marked increase/

increase of fibrous tissue around the portal vein ramifications.

The portal vein system, from trunk to peripheral branches, was blocked by an old, dry, and rather hard thrombus so completely that it was difficult to find any places not so obstructed. This reddish-brown thrombus, which showed laminal arrangement, had become adherent to the rough and irregular intima. In the walls of the veins the microscope revealed eggs deposited in rows, with a little round-celled infiltration in the neighbourhood.

The changes found in the intestines corresponded with those already recorded in connection with the other cases.

The spleen measured 16½ x 11 x 4 cm. Its capsule was much thickened and wrinkled. Cut section showed hyperplasia of the connective tissue. The changes in the spleen were probably, in large part, due to severe and chronic venous congestion of the organ.

The foregoing descriptions of the pathological changes found post-mortem in cases which have died of schistosomiasis have been taken, for the most part, from the few published papers of eminent workers who have made a special study of the disease, both in China and Japan. Their accounts agree with one another, and further repetition would be unnecessary. Before closing this section, however, I should like to refer to one more case because it shows how unusual lesions may be found in unexpected/

unexpected places according to the manner in which the ova of the parasite happen to have been distributed.

This was a case from Katayama, Japan, and described by Tsunoda. The necropsy revealed, besides the ordinary lesions in the liver, etc., thickening, with haemorrhagic infiltrations, of both the dura and pia mater. In the brain itself wedge-shaped sclerosed areas of greyish colour and surrounded by ecchymoses were found. In the lenticular nucleus, optic thalamus, and internal capsule of the left side, there was an area of softening the size of a walnut. These areas were found to contain ova embedded in neuroglia and surrounded by softened and degenerated brain-tissue. The patient during life suffered from disorders of speech, tremors, headache, and mental disturbance; later from vertigo and Jacksonian fits (two or three a day), and finally from right hemiplegia.

Resumé of the Pathology.

(a) Post-mortem examinations reveal the fact that the worms live in the portal vein, and in its tributary branches and radicles.

(b) The main pathological feature is an embolic process, the ova of the parasite being the emboli. Eggs deposited in the venous radicles in the intestinal walls, and also in the larger veins, are carried in enormous numbers to the liver, in which organ they are, as it were, filtered off, and block the capillary terminals/

terminals of the portal vein.

(c) On this account, and aggravated by the toxaemia which is a direct result of the parasites' presence in the body, secondary tissue changes are set up in the liver, notably round-celled infiltration and hyperplasia of the connective tissue, which later becomes converted into fibrous tissue. Later still, owing to the contraction of this fibrous tissue, the vessels become still further obliterated, and the liver, which was at first enlarged, becomes a shrunken, hard and cirrhotic organ.

(d) The effect of this obstruction to the flow of blood through the liver is seen in ascites, in chronic venous congestion of the stomach, spleen, and intestines, and in all the signs which we associate with stasis of the portal blood.

(e) The irritating presence of the parasites in the portal vein and its tributaries is apt to set up endophlebitis, causing a roughening of the vein lining, and this combined with the blood stasis may result in the formation of thrombi, as in Case 3 recorded by Tsuchiya.

(f) Splenic enlargement, so frequent a feature of this disease, I am inclined to ascribe to the severe toxaemia which results in hyperplasia of the connective tissue. In addition we have chronic venous congestion of the organ.

(g)/

(g) The eggs which the parasites lay in the wider vessels are, as we have seen, carried by the blood-stream to the liver; but eggs which have been deposited by parasites wedged in the smaller radicles of the portal system in the intestinal walls ultimately cause rupture of these vessels and both blood and ova escape into the submucous tissue. From thence the eggs are carried by the lymphatics to the mesenteric glands, giving rise to the great changes which we find in these organs.

(h) The breaking-down of the mucous membrane in patches may also be ascribed to this cause, i.e. to the plugging of the vessels by the parasites and their ova, whereby, not only do we get the sequence of events recorded above but even before that, small areas of the mucosa become congested, their nutriment impaired, and their vitality so lowered that they become a prey to bacterial invasion from the bowel, necrosis follows, and both blood and ova find their way into the lumen of the gut.

(i) As in the liver, so in the intestinal wall, and in other parts where groups of ova are deposited, tissue changes are excited, the round-celled infiltration surrounding the colonies of eggs becoming converted later into fibrous tissue. Great thickening and hardening of the large intestine, in whole or in part, may result from this cause; and the retro-peritoneal glands/

glands may become greatly enlarged, matted, and massed together. The "tubercles" found in the submucosa or under the serosa of the bowel, and in other places, originate in a similar manner, the same tissue changes occurring around isolated groups of eggs.

(j) A comparatively few eggs succeed in filtering through the capillary meshwork of the liver, to emerge into the vena cava and so to the heart. From thence they may be carried by the arterial blood to distant parts of the body, and become lodged in terminal vessels in the lung, in the kidney, or even in the brain.

CLINICAL FEATURES.

I trust that, from the foregoing account, a fairly accurate conception will have been conveyed of the pathological changes which take place within the body as a result of its invasion by the blood-worm S. japonicum. The gross lesions are very different from those which we find in cases of Egyptian schistosomiasis, where the bladder and rectum are chiefly involved, and in which, as a consequence, we get a corresponding symptomatology - severe dysentery, dysuria, and haematuria. In Asiatic Schistosomiasis, as will be readily appreciated when we consider the pathology of the affection, the symptoms may be said to be, in the main, those of *portal obstruction*. We have, undoubtedly, the initial signs and symptoms of infection, such as malaise, fever, and

and urticaria; we have also, in response to the toxins liberated by the parasite, marked changes taking place in the blood; but, as the disease advances, portal obstruction becomes increasingly evident, and backward-pressure phenomena more and more accentuated. Thus we get chronic venous congestion of those organs whose blood drains into the portal system, viz., the spleen, stomach and intestines. There is chronic gastric catarrh, dyspeptic trouble, irregular diarrhoea, ascites, general malnutrition, and progressive weakness, in short the whole train of clinical phenomena associated with a cirrhotic liver. In addition dysenteric troubles due to the local effects of the parasite on the bowel wall manifest themselves, and a profound cachexia develops as a result of the deleterious influence of the parasitic toxin present in the blood.

The clinical manifestations of a well-marked case of S. japonicum infection are, therefore, quite characteristic and readily recognised by one accustomed to deal with this affection. The patient walks into the consulting-room with an obviously wearied look. He is emaciated, evidently deficient in muscular force, and glad to drop into the proffered chair. One sees at a glance, even before the clothing is removed, that the abdomen is distended, and it needs but a touch on the two flanks to elicit the thrill of fluctuating fluid. Further examination reveals an enlarged liver and spleen. Inquiry will now discover that the patient is a farm labourer or

a/

a boatman and that he has suffered for some time from dysentery or from troublesome diarrhoea. The patient complains chiefly of the swollen belly, the dysenteric symptoms, and dyspepsia, and this, associated with the characteristic "weary" look, enables the physician to form a very definite opinion as to the nature of his patient's malady. An early opportunity will be taken to examine the stools microscopically when the finding of the characteristic miracidium-containing ova will complete the diagnosis.

Although the above represents a typical well-advanced consulting-room picture of the disease, there are, naturally, many deviations from this type case, the variations depending upon the degree and the duration of the infection.

In order, therefore, to get as complete an account of the clinical features as possible it is necessary to study the affection from its inception, that is, as soon as the earliest symptoms manifest themselves. Unfortunately Chinese patients do not present themselves to the foreign doctor early enough to give an opportunity of studying these initial stages. We have learnt all we know of the primary symptoms of S. japonicum infection from the clinical history of those foreigners (notably British and American) who, while resident in the Yang-tse valley, have been unfortunate enough to contract the disease.

For/

For a number of years physicians residing in mid-China have time and again been puzzled by a strange endemic fever, the true nature of which completely eluded them. Its origin was entirely unknown, and the nebulous state of our knowledge on the subject may be guaged by the fact that the fever was variously and loosely designated, according to the locality in which it occurred, as "Hankow fever", "Kiukiang fever", "Yang-tse River fever", and so on. Early in 1910 Lambert[16] of Kiukiang described the condition with considerable care under the term "Urticarial Fever, occurring in the Yang-tse Valley". At the time that he wrote his paper on the subject, Lambert could assign no definite specific agent as the cause of the trouble, but he had observed that there appeared to be "a definite relationship between physical contact on the part of the patient with the mud in the paddy-fields and creeks and shallow lakes emptying into the Yang-tse, and the subsequent development of the disease a few days later". He noticed that the fever appeared to be contracted only by those who exposed the naked skin to the muddy water, e.g. gun-boat officers and men who, in their shooting expeditions, would wade bare-legged in the marshes and lakes after the ubiquitous snipe. He observed that those who did not remove their stockings and puttees escaped the fever. He was therefore of the opinion that the disease was derived from the water and was probably conveyed by the bite of some water insect or fly.

In/

In describing this fever Lambert states that from ten to fourteen days elapse from the time of infection to the time of invasion of symptoms. The premonitory symptoms are variable. There is usually headache and malaise; the temperature rising from 100° - 103°F. Sometimes abdominal symptoms are present, such as epigastric pain, vomiting and diarrhoea, before the characteristic rash comes out. Or there may be no premonitory symptoms, the rash being the first sign noticed by the patient. This rash, which is of an urticarial type, may appear in any part of the body. The wheals are at first small white raised areas which rapidly increase in size until they may measure three or four inches in diameter. Frequently the wheals, which are dead white in colour and which may remain "out" for an hour or two, [illegible] [illegible] grey area of [illegible], and there is a pinkish areola around. "As they disappear the central part clears up first, the areola fading last of all, so that on examination of the patient one finds the patches in all stages of development, from the early wheal, as large as a sixpence, to sinuous, raised, red lines, the outlines of former areas, some of which measure several inches in circumference."

The eruption appears and disappears in an erratic manner for a week or more and then subsides. It rarely persists more than a fortnight. It does not cause any particular irritation when "out", and leaves no mark when it has passed away.

The

The temperature is usually normal in the mornings, but rises in the evenings to about 102° F. and then gradually falls again.

The rash and the temperature do not apparently bear any special relationship the one to the other, the temperature frequently continuing for many days after the rash has completely disappeared.

The pulse usually remains about normal.

The urticarial rash, that is, these same areas of local oedema, may invade the mucous membranes, as of the nose, mouth, and throat, causing a watery discharge and temporary impediment in respiration.

Cough is a not infrequent symptom, accompanied by more or less secretion. Moist râles may be heard, and there is expectoration. There may be dullness over one or other base, and fine crepitant râles. If the lungs be frequently examined they show patches of dullness with distant breath sounds, and these dull areas come and go in a remarkable manner. They may clear up in one place within a few hours, only to involve some other and quite distant portion of the lung. They are due to patches of oedema on the pleura or in the alveoli of the lungs, in the same way as on the mucous membrane or on the skin. Exudation from these would cause the secretion and expectoration. There may even be distressing symptoms of dyspnoea and dyaphagia.

Examination of the sputum is negative.

Urticaria

Examination of the blood shows a steadily increasing eosinophilia, which may reach 50% or even more. Anaemia progresses if the case is a long one; the red cells may be 3,000,000 per c. mm. after three weeks fever. At first the white cells show an increase, but later on there is a reduction to about 6000 per c. mm., the reduction being mainly in the polynuclears.

No organism could be discovered microscopically in the blood, sputum, or urine.

Urine is diminished in quantity, and of high specific gravity. No albumen.

The liver and spleen may be enlarged.

Duration. In mild cases the fever disappears in about ten days, but it will be a month before the patient recovers normal health. In more severe cases, fever of a remittent type may last a month or six weeks. Health may be regained in about three months.

The condition as above described is a well-known trouble in Central China, and officers and men from the gun-boats stationed at different ports along the Yang-tse are specially prone to come down with this fever during the hot Summer months.

The clinical combination of fever, cough, urticaria, diarrhoea, form a group of symptoms often very puzzling to medical men who are called in to attend these cases, and the diagnosis is very difficult to those who are not acquainted with the trouble. Some of the cases are suggestive/

suggestive of pulmonary tuberculosis, others of typhoid. The connection between the sickness and a history of wading in ravines is, however, so constant as to suggest that the one stands in a causal relationship to the other. To Lambert, everything pointed to an infection derived from the water, perhaps a verminous infection, the embryo of the unknown worm, as in Ankylostomiasis, penetrating through the skin. Besides the association with water, the eosinophilia was also suggestive of such a theory; and the nature of the fever, accompanied by "urticaria", seemed to point to some toxin circulating in the blood. The link between these comparatively mild cases in foreigners and advanced schistosome infection as met with in the Chinese, did not occur to anyone. Nor is this surprising, for apart from the fact that the former appeared to occur only in foreigners and the latter only in natives, the clinical pictures presented by the two conditions were certainly not such as to suggest identity. Little did Lambert, or anyone else, at the time, suspect that these puzzling cases of "Yang-tse river fever" were, in reality, incipient cases of Asiatic schistosomiasis.

In March, 1911, Logan[17] reported a case of S. japonicum infection in an American boy, aged 13. The boy had returned from America, in excellent health, with his parents, in March 1908, and lived at Yo-chow, a town situated at the North-east corner of the Tung-ting lake, in the province of Hunan. His favourite pastime was

wading/

wading or bathing in the lake. During the latter part of July of the same year he was taken with diarrhoea, which was followed two days later by a rash on the face, neck and arms, also large blotches on the arms, legs and body. The wheals were pale, and elevated nearly quarter of an inch above the surrounding skin. A little blood appeared in the stools. Fever was also present and lasted for six weeks, when the patient gradually regained a measure of health. During the winter which followed he kept fairly well, but blood was passed in the stools at intervals of three or four weeks. There were also occasional attacks of fever.

In the Spring of 1909 the patient had dysenteric symptoms steadily for about a month, and continued to pass bloody stools intermittently. During the Spring and early Summer of this year the lad waded a great deal in the ponds of the neighbourhood, and swam in the lake. Early in July he became very ill with fever and dysentery, being confined to his bed for three weeks.

In the Spring of 1910 the symptoms were similar, but he continued wading and swimming in the ponds. On one occasion, after wading in a pond in July of this year, he noticed a papillary rash on both legs up to the knees. A week later he was taken ill with a bad headache and fever, with vomiting and abdominal pain. The next day, July 11, the pain was very severe and the fever high. The temperature remained high, from 103° - 104° F., for a week, the abdomen was very hard, and breathing difficult -

due/

due apparently to peritoneal irritation or inflammation. He was taken to the mountain sanatorium at Kuling on July 22, and Dr. Logan saw him there on the 24th.

Having obtained this history of the case from the boy's parents, Logan examined his abdomen and found it soft but slightly tender. The liver and spleen did not present any enlargement. Digital examination per rectum revealed thickening for two and a half inches inside the sphincter, feeling like a ring with a small lumen and papillomata, instead of normal mucous membrane. Microscopical examination of the stools revealed great numbers of eggs of S. japonicum.

A differential leucocyte count on September 3 showed:-

Polymorphonuclear	Leucocytes	48%.
Large Mononuclear	"	16%.
Small "	"	16%.
Eosinophile	"	20%.

With regard to the diagnosis, this was put beyond any manner of doubt by the finding of Schistosome ova in the dejecta. Logan's opinion is that the boy must have contracted the disease via the skin as he never drank any water but that which had been boiled in his own home. The boiling of all drinking water is very stringently insisted on by all foreigners resident in China, and it is practically certain that the boy never drank water taken directly from the lake or from the ponds in which he waded.

He/

We come now to the link which connects the obscure fever of the Yang-tse valley with infection by S. japonicum. It was Dr. Houghton, then of Wuhu, who first suggested the connection. Houghton was called in consultation in the above case of the American boy, and on getting the history of the urticarial rash as already recorded, he drew Logan's attention to the similarity between the cutaneous signs in this case and those of Lambert's wading patients. Was it possible that the latter had also been suffering from schistosome infection? The importance of linking "Urticarial fever" with S. japonicum, of suggesting that "Yang-tse River fever" might in reality prove to be incipient schistosomiasis, can hardly be over-estimated. The idea was taken up by Lambert and others, and in following up the idea quite a series of cases were collected in which exposure to contaminated waters resulted in this urticarial attack with fever and other symptoms, to be followed, after an interval of a month or six weeks, by the appearance of schistosome ova in the stools. Thus a considerable advance was made into some of the dark regions of unknown fever-land. Many cases of "Yang-tse River fever", "Hankow fever", and "Kiukiang fever", and most cases of "Urticarial fever" in endemic areas, became plain as an open book. Writing in September 1911 Lambert[10] shows that the same cases which he formerly described under the title "Urticarial fever" were in reality cases of incipient/

incipient schistosomiasis. Acting on Houghton's suggestion, he examined in July 1911 the faeces of one of these patients, one who, after wading after water-fowl in the vicinity of Kinkiang in November 1909, came down, fifteen days later, with "Yang-tse river fever". The case had been a typical one, with the urticarial rash and eosinophilia. On the top of an otherwise normal stool Lambert noticed a small streak of blood-stained mucus, and on examining this microscopically he found the eggs of S. japonicum.

With regard to the early diagnosis of Schistosomiasis, the urticarial rash is by no means always present, and when present is of diagnostic importance only when taken in conjunction with the history, the fever, and the eosinophilia. The combination of these three should arouse suspicions, which would be confirmed by microscopic examination of the faeces.

It certainly is of the first importance to be in a position to diagnose S. japonicum infection in its early stages. Lambert would make the following combination of events the criterion by which a case of incipient schistosomiasis may be recognised, before ever the eggs appear in the stools. (1) History of bathing or wading in the shallow lakes and back-waters in the vicinity of the Yang-tse. (2) Thereafter an incubation period of ten to fifteen days. (3) Then fever, rising in the evening to 102°F. or higher, followed by profuse sweating, and a gradual return to normal in the morning.

Generally/

Generally, the higher the temperature the more severe the infection. (4) Blood examination shows from the commencement of the attack a marked and increasing eosinophilia, reaching to as high as 60% in some cases.

The above points are of importance. Other symptoms, such as cough, abdominal pain, and diarrhoea, vary considerably. The urticarial eruption is present in perhaps 50% of the cases.

Later on dysenteric symptoms appear and are sometimes marked and distressing. Ova of the parasite may be found in the bloody mucus. Katsurada's observations on experimentally infected animals would go to show that ova may be found in the stools within one month of infection. But absence of dysentery, and failure to find eggs in the stools, by no means negatives schistosomiasis. Though eggs can usually be found sooner or later, in not a few cases repeated search has proved negative even after centrifugalising the specimens. These are cases of less severe infection where, presumably, the parasites are not present in the veins of the intestinal walls in any great number, but are located in the larger veins, as the mesenteric, and consequently the ova pass, for the most part, to the liver. Thus a diagnosis has sometimes to be made from other data, and apart from the discovery of ova.

The spleen in these incipient cases is nearly always somewhat enlarged.

The liver may be slightly enlarged, with a feeling of weight and discomfort in the hepatic region.

If/

If the infection is not a heavy one, and if the patient does not expose himself to re-infection, the body becomes tolerant of the comparatively few parasites present, and the symptoms gradually disappear.

The experiences of other physicians residing in the Yang-tse valley coincide with Lambert's. The latter[18], in a paper published in the Transactions of the Society of Tropical Medicine in November 1911, quotes from a letter which he had received from Dr. Aird of Hankow. In his letter Aird mentions two cases, Europeans, who had recently settled in Hankow. "Both went bathing in shallow water on the flooded plain; both developed fever about the same time and were admitted into hospital. Blood examination showed a high eosinophilia in both, which suggested a possible infection with worms, and on examination of the stools the eggs of S. japonicum were found abundantly present in both. One patient showed some transient urticaria, but the other showed none at any time. The fever was of a swinging type, 99° to 100°F. in the morning, rising to 102 or 103° or over, towards evening, and after about a fortnight it declined by lysis."

Thomson tells of a party of twelve foreigners who went bathing in a shallow lake near Hankow. Of these twelve men, three, not being swimmers, spent their time in the shallows near the bank, wading, dipping, and splashing. These three subsequently developed fever, headache, and malaise. Two showed giant urticaria. All had/

had a pronounced eosinophilia. There was enlargement of both liver and spleen. In all three schistosome ova were discovered in the stools. Three others of the party swam from their boat to the shore, and paddled a little in the shallows; and of these latter three, two had fever with marked eosinophilia, 30% - 40%; the third had eosinophilia without fever or other symptoms. These three showed no ova in the stools, and taking their history into account, and the fact that they did not remain long in the shallow water, might justifiably be considered as cases of slight infection. The six other bathers appeared to be unaffected; they swam in the deep water round about the boat and did not go in the warm shallow waters close to the shore.

In April 1912 Fleet-surgeon Bassett-Smith[20] describes a case which came into his hands in London. The patient, a European aged 24, who was serving in a man-of-war up the Yang-tse, while at Hankow went bathing with four others in a creek on June 16th, 1911. All were subsequently attacked with fever, three out of the five so severely that they had to return to England. In September the patient showed a marked eosinophilia, with high total leucocyte count. The red cells were diminished. The liver was slightly enlarged. Large ova containing living embryos were found in his stools. On arrival in England in December, six months after onset of disease, he looked ill, felt weak, and was somewhat emaciated. There was slight oedema of the ankles. Examination

Examination of the stools revealed ova of S. japonicum. The leucocytosis was still present, and a differential count showed that the eosinophiles had reached 60%. Later, as the patient improved, the eosinophilia became less marked and the polymorphonuclears correspondingly rose.

Writing in the "United States Naval Medical Bulletin" for January 1914, Laning[21] gives an account of seven cases of schistosomiasis which occurred on board the U. S. gun-boat "Quiros" while anchored off Yo-Chow and Changsha in the Hunan province. The ship was at Yo-chow, a heavily infected locality, from July 12 - 14, 1913. On arrival at this port orders were given that no swimming would be allowed. On the 13th, however, several of the men managed to evade the medical officer and went swimming in a pool near to the shore. On the 14th three men developed typical symptoms of incipient schistosomiasis.

The ship went on to Changsha on the 14th and the next day another clandestine swimming party was formed. Between twenty-four and forty-eight hours afterwards a second group of cases came down with the characteristic symptoms.

These cases are of importance as showing that the incubation period is only from twenty-four to forty-eight hours, and not, as Lambert supposed, some ten or more days. This certainly is more in accordance with what one would expect under the circumstances.

Laning/

Laning gives a full account of his seven cases, and the symptoms were much the same in all. A definite history of bathing in infected waters was definitely established in all. All had abdominal pain, particularly in the hepatic region. In the mornings his patients felt fairly well, but in the latter part of the day they felt weak, dizzy, and feverish. The temperature rose to 105°F. in three of the cases. Headache, cough and diarrhoea were very commonly present. The urticarial eruption was present in four cases. Eosinophilia was present in every case and averaged about 50%. Ova were found in the stools in one case presumably 12 days, and in another 23 days, after exposure to infection. The liver and spleen in these two cases were perceptibly enlarged three weeks after infection, when the eosinophiles had risen in the one case to 76% and in the other to 68%. The liver was perceptibly enlarged in four cases out of the seven, and the spleen in three cases, three weeks from the beginning of the illness.

These are but samples of quite a number of foreign cases that have been infected by this blood-worm during residence in Central China. They represent the initial stages of the disease, and are met with commonly enough in Europeans and Americans, but not in the Chinese, who do not come to hospital early enough to show the primary signs of infection. As a rule the natives will only consult the foreign doctor when they are seriously ill and/

and incapacitated. In the case of the Western resident, medical assistance is summoned early, and the patient being warned of the source of infection avoids re-infection, and after the preliminary reaction of the system to the parasites the body becomes tolerant of their presence, symptoms gradually subside, the eosinophilia falls, and the patient ultimately regains good health, though he may be harbouring a number of living worms in his portal system.

In the case of the Chinese coolie the matter is very different. Doubtless he goes through the stages which we have termed Incipient Schistosomiasis, but as soon as he is fit, and probably long before he is fit, he is back again at his old occupation, whether it be fishing in the creeks or planting rice in the flooded paddy-fields. Constantly wading in the contaminated water of his village he exposes himself to infection over and over again. Thus it is that the very numerous cases seen among the Chinese are nearly always cases of long-standing and of heavy infection. Even so, some are much heavier than others, and the signs and symptoms of the disease will vary accordingly. Indeed, the clinical picture varies within somewhat wide limits, and depend not only upon the degree of infection sustained by the patient, but also (because the pathological changes are progressive) upon the stage in the history of the trouble which the patient has reached. Thus, in a fairly recent though heavily infected case, there may be an/

an enormously enlarged smooth liver, the result of inflammatory hyperplasia of the interlobular connective tissue, but, as yet, no ascites. As the case progresses, however, the liver shrinks again owing to formation and contraction of the fibrous tissue, and the organ presents the physical signs of a small, hard, nodular, and cirrhotic liver. As the changes in the organ become sufficiently advanced, and the portal terminals become more and more blocked with ova, fluid makes its appearance within the peritoneal cavity, the ascites ultimately progressing to the most extreme and distressing stages.

There are other atypical and unusual cases which are occasionally to be met with among the Chinese, and an account of this disease would not be complete without some reference being made to these cases. In some instances neither the liver nor the spleen may show any appreciable enlargement or tenderness, or any other change. There may be no dysentery, stools may be fairly regular, and ova difficult to encounter owing to their sparsity. One may fail entirely to find eggs in the faeces and the diagnosis has to be made upon other grounds, notably the high grade of eosinophilia. These are cases of comparatively slight infection but of long duration, cases which, contrary to the rule, have not perhaps been much exposed to infection and who have come to hospital for other conditions altogether. They more nearly approach the type of case met with in foreigners after/

after the lapse of an interval of time.

Tsuchiya[14] lays stress on the stunting of the physical development in those cases where the disease is contracted early in life. Such patients fail to attain maturity of stature, and are frequently miserably undersized. They show plain evidences of malnutrition and anaemia, and are greatly lacking in functional activity and in bodily energy. In the later stages the structure of the chest-wall undergoes changes. Owing to the enlargement of the liver and spleen and the greatly distended belly, the lower costal cartilages are widened out, so that they form a very obtuse angle where they meet together in the mid-line, and run nearly horizontal. The circumference of the lower half of the chest cavity is considerably increased. Longitudinally the cavity is much shortened, but widened transversely, the more so the nearer one gets to the diaphragm. The functions of both heart and lungs may be seriously impaired by the upward pressure caused by excess of fluid in the peritoneal cavity. There may also be compression of the inferior vena cava causing oedema of the lower half of the body.

On account of the portal obstruction we get a compensatory dilatation of the venous collaterals of the abdominal wall, but this is not so marked as in other cases of hepatic cirrhosis.

Chronic venous congestion may give rise to haemorrhage/

haemorrhage into the stomach and haematemesis as in the case of Tsuchiya's which we have recorded. But it is not a frequent complication.

Jaundice, caused by fibrous compression of the bile ducts, is seldom met with, the cirrhosis being in the main peri-vascular.

The nervous system is not, as a rule, appreciably involved in schistosomiasis, apart from the general weakness, which may be extreme, and which I think is in a large measure referable to the anaemic and toxaemic state of the blood. Houghton has, in the earlier stages, frequently found the knee-jerk much exaggerated. In late cases I have sometimes found the contrary condition, the patellar reflex being unusually sluggish.

Although certain cases have been reported which exhibited brain symptoms and in which post-mortem examination afterwards revealed cortical and other lesions containing schistosome ova, such cases are certainly very rare.

Houghton[9] mentions the occasional incidence of cases showing a high degree of eosinophilia and cerebral symptoms, but, though the association is suggestive, a relationship cannot be said to be proved between the trematode infection and the cerebral condition.

Cases of schistosomiasis japonica are, as I have already indicated, extremely numerous among the Chinese living in endemic localities. They conform, for the most/

most part, to one main classical type, and are readily diagnosed by physicians who have become familiar with the clinical manifestations of infection by this noxious parasite. I recognised my first case in November 1907; others followed, and I was able to make a careful study of the clinical features of the disease. As very little was known, at that time, of the symptomatology of the affection I wrote a paper on the subject which was published in London in March 1909[5], and which represents, so far as I am aware, the first full account (in the English language) of the signs and symptoms of Asiatic schistosomiasis. It will not be necessary for me to repeat what I recorded in the paper referred to, as the points have already been brought out in the present Thesis. I will here give only the summary with which I concluded my remarks on the clinical aspects presented by my patients.

Summary of the Signs and Symptoms.

(1) History of fever.

(2) History of dysentery.

(3) Abatement of dysenteric symptoms, but in their place an irregular diarrhoea, showing a large amount of undigested food, and a little blood-stained mucus.

(4) Microscopic examination of the faeces, and especially of the blood-stained mucus, reveals ova of Schistosoma japonicum.

(5) Marked dyspeptic symptoms.

(6)/

(6) Enlargement and may be tenderness of liver and spleen.

(7) Ascites, and other signs of portal obstruction.

(8) Listless, wearied expression.

(9) Extreme weakness, lassitude, and disinclination (even inability) for physical or mental effort.

(10) Malnutrition.

(11) Temperature subnormal during the day, but sleep is disturbed by fever and restlessness.

(12) Marked eosinophilia.

The list conjures up the clinical picture presented by a large number of these cases, and there is little to add to it. It may be taken to represent "a type case" of fairly heavy infection in a Chinese. It is not, however, complete without qualifying remarks, for, as already stated, the picture shows variations according to the degree and duration of infection. The above represents commonly met with severe infections at a fairly advanced stage, but not so late as when the liver shrinks and ascites becomes extreme.

Laning[45] has attempted to divide the progress of the disease into "three stages", though, of course, any hard and fast division of this kind must, in the nature of the case, be purely arbitrary. It is, however, not without interest, and I reproduce it here as it serves to bring out the main features presented by patients at different stages of their clinical history.

(1) The initial stage, marked by a high afternoon temperature/

temperature, lasting from three to six weeks; comparatively slow pulse; oedemas and urticarias, with evanescent areas of pulmonary dullness; cough; pain in the abdomen; diarrhoea; eosinophilia. Ova may appear in the stools about the third week.

(2) The second stage is marked by an enlarged liver and spleen; loss of weight; irregular fever; pronounced eosinophilia and some anaemia; and the passage, with more or less tenesmus, of blood-streaked mucus containing the ova of the parasite. This stage lasts, roughly, from three to five years, (varying according to the severity of the infection), before the third stage supervenes.

(Foreign patients, because they are warned and avoid re-infection, usually recover after some months in this stage. The fever, eosinophilia, and other troubles gradually disappear. But it is far different with the Chinese who, in their daily work, are being continually re-infected. In them the disease progresses to its terminal stage.)

(3) The third stage is marked by a cirrhotic liver, sometimes enlarged, but later still shrunken; ascites; oedematous extremities; marked emaciation; anaemia and great weakness; an irregular diarrhoea with exacerbations of dysenteric symptoms; ova in the stools; eosinophilia; much restlessness and may be fever at nights. The ascites and other symptoms become aggravated to the most extreme and distressing limits/

limits, and the patient ultimately dies from exhaustion or he is cut off by some inter-current terminal infection.

We must, of course, regard these "stages" as an expression of the point which has been reached by the patient in the pathology of the affection. We have first the stage of invasion, coming on almost immediately after infection, when great numbers of living embryos are finding their way through the skin, into the lymphatics, and general circulation, and crowding into the liver; from thence making their way into the portal venous system, and beginning to lay their eggs. This stage is characterised by pronounced systemic reaction to the invasion of the parasite, which is shown by febrile disturbance, remarkably high eosinophilia, an urticarial eruption - and with all the symptoms we associate with incipient schistosomiasis. The toxin liberated by the parasite results also, after some three weeks, in inflammatory hyperplasia of the connective tissue, and in enlargement and tenderness of the liver and spleen.

As the disease progresses and the pathological lesions become more severe, the clinical signs will indicate the changes that are going on within. On account of the progressive changes taking place in the liver, the deposition therein of crowds of ova, and the formation of fibrous tissue, the symptoms become largely those of portal obstruction. Chronic venous congestion of/

of spleen, stomach, and intestines supervenes, with chronic gastric catarrh and dyspeptic trouble, irregular diarrhoea, general malnutrition, and weakness. Ova also settle, as we have seen, in the mesenteric glands and intestinal walls, resulting in ulceration of patches of the mucous membrane of the large bowel, and dysenteric symptoms become marked.

Still later, as a result of the blocking of the terminals of the portal vein by ova-emboli, and contraction of the fibrous tissue, ascites makes its appearance and is progressive.

Later still, marked contraction of the fibrous tissue in the liver takes place, we get a hard, shrunk-up cirrhotic organ, effectually damming back the portal current, and, as a consequence, the abdomen gets enormously distended with ascitic fluid rendering the victim absolutely helpless; nutrition fails; wasting becomes extreme; and, the vital functions running out, the patient succumbs in a state of complete exhaustion.

Before leaving this section on the clinical aspects of Asiatic Schistosomiasis I should like to call attention to a peculiar feature of the disease that I have noticed in well-advanced cases, especially in those cases where diarrhoea and dysentery are prominent symptoms. The point to which I refer is the marked improvement which takes place in the patient's condition during the Winter months. Throughout the cold season, from October to

March, he enjoys much better health, but when the Spring and early Summer come on there is a decided relapse, the dysentery returning with all its old virulence, bloody mucoid stools being again passed with great frequency and with much straining and pain. This apparently happens independently of any re-infection, for it starts early, i.e. before the patient returns to his rice-fields, or has begun again, in the course of his avocations, to wade in infected waters.

I can only account for this on the assumption that in the warm Spring months there is renewed activity on the part of the parasite, eggs are again actively extruded, and these, deposited in the tissues of the intestinal wall in ever-increasing numbers and in the manner already described, result in a recrudescence of the dysentery. It seems to me that this is entirely in accordance with what we might expect if we consider the question from the point of view of the parasite's economy. Eggs are not laid by the worm and passed out via the intestinal canal of the host in any great numbers during the Winter months, for such eggs would be doomed to perish. They could not possibly survive the low temperatures obtaining at that time of the year; for even in Central China and Japan the temperature during the Winter months frequently falls to freezing point, and often is considerably below this. The parasite reserves its reproductive energies until the warm months of the year/

year come round again, when the ova, passing out of the host in prodigious numbers, and reaching water at the required temperature, may find opportunity for further development. Under suitable conditions the miracidia readily hatch out and take the first opportunity of effecting an entrance into man, their definitive host. In this way, in the interests of its own economy, the parasite safeguards the propagation of its species.

THE BLOOD.

An account of the clinical features of Asiatic Schistosomiasis would not be complete without reference being made to the condition of the blood.

It has already been made clear that this parasitic worm takes up its abode in the veins of the portal system. This has been proved beyond any manner of doubt, for post-mortem examinations have demonstrated them in great numbers in the portal tributaries. As the adult worms do not leave the blood-vessels, but live permanently in them, they must derive their nourishment from the blood itself. The ingestion by the parasite of the blood of its host necessarily involves a mechanical destruction of blood-cells, and this can be on no small scale when we remember that there may be many thousands of worms present. This alone is sufficient to account, in part at any rate, for the anaemia, and for the deficient number of red cells found upon examination of the blood. Both the reds and the whites are diminished.

diminished in number.

There can be little doubt, also, that in addition to destroying the healthy blood cells, and returning excrementitious matter, the parasites secrete a toxin, which being constantly elaborated and supplied to the blood keeps it in a perpetually poisoned condition. It is this toxaemia which, I believe, is responsible, among other troubles, for the lassitude and weakness, the fever and malaise, and which determines the early splenic and hepatic enlargement. The swelling of the liver and spleen become noticeable about the third week after infection, when the parasite has grown to the adult stage, and the toxins have accumulated in sufficient concentration to produce this change. In other words, the severe toxaemia causes an inflammatory hyperplasia of the connective tissue of these organs. I think the early enlargement of liver and spleen must be accounted for in this way, for there has been no time for any great deposition of ova, which, by irritation, could produce so rapid an hypertrophy. Again, the spleen frequently partakes in this enlargement, even though no eggs are deposited therein. I say this as regards the initial enlargement. Later, the crowds of ova deposited in the portal terminals of the liver result in a peri-vascular cirrhosis of the organ. Katsurada, apparently, is of the opinion that the hepatic changes are due entirely to the irritation produced by the ova. On the other hand, Phalen/

Phalen and Nichols ascribe the cirrhotic condition, both early and late, to the toxins liberated by the parasite; thus making it analogous to the pathological changes produced by other poisons, such as alcohol, where also we get first a hypertrophic to be followed later by a coarse atrophic cirrhosis.

The Red cells are found to be diminished in number; the average may be taken as 3,000,000 or 3,500,000 per c.mm.

The White cells at first show some increase, but later there is a reduction, which is mainly in the polymorpho-nuclear leucocytes. The total number of white cells may be found to be about 6,000 per c.mm. This diminution in the polymorpho-nuclears presumably lessens the defensive power of the body against infective micro-organisms; and, indeed, we find these patients make very bad cases for any kind of surgical procedure.

The most characteristic change in the blood, however, is the pronounced eosinophilia. A percentage increase in the number of eosinophile leucocytes is, of course, very constantly found in the blood in other helminthic infections. "Helminthiasis is, above all", as Weinberg says, "an intoxication. . . . . . produced by the toxic products which the parasite secretes", and this change in the blood which we term "eosinophilia" is, it seems to me, brought about by the action of the verminous toxin on the blood-forming organs. It represents the reaction of the blood to the toxin. Thus we get this blood/

blood-change in all worm infections (as well as in some other impure blood conditions), but the change would seem to be peculiarly marked and persistent in schistosomiasis.

I have seen it suggested that the higher the eosinophilia the more intense is the infection by S. japonicum, but I am by no means satisfied that this is the case. A high eosinophilia *may* indicate a high degree of infection, but, to my mind, it is to be taken rather as an index of the blood-reaction. The patient's susceptibility and powers of resistance have to be taken into account. A vigorous reaction, with a high eosinophilia, indicates the high resisting powers of the patient, rather than an exactly corresponding degree of infection; though it may be true, in the main, that a high degree of infection will generally stimulate a high resistance.

But that this is not always so is shown by the fact that the degree of eosinophilia will vary considerably in the same patient at different times; and also, in long-standing severe cases which are approaching their end, the patient's resistance to the toxin may break down. He can no longer put up any fight against the enemy. This is shown by a failure in the blood-reaction, and disappearance of the eosinophilia. It is of ominous portent and leads up to a fatal issue.

In a paper on Ankylostomiasis, Bryson[31], who has had considerable experience of this disease in the Chinese province of Honan, says "Eosinophilia is nearly always marked. A point with regard to eosinophilia in this/

this disease should be mentioned. Recently a miner died of ankylostomiasis in hospital. The eosinophilia was 42% in July last, when he refused treatment, but on his return on December 14th, (the day before his death), the eosinophilia had vanished. . . . . . . A low eosinophilia in an advanced stage of the disease is of bad prognostic import."

I have seen the same thing in schistosomiasis japonica. In a bad case of this infection that was nearing his end in my hospital, a differential blood-count showed 54% polymorphonuclear leucocytes, and 46% of lymphocytes; no large mononuclears, and, strange to say, not a single eosinophile leucocyte; showing that the patient's resistance to the verminous toxin had completely broken down.

We find an interesting parallel to this in some micro-organismal infections, as, for example, in fulminating cases of pneumonia, where a failure in the blood-reaction, as evidenced by an absence of polymorphonuclear leucocytosis, indicates a very low state of resistance on the part of the patient.

In Incipient Schistosomiasis, as the toxins increase in concentration, the reaction of resistance also becomes more marked, and we get a gradually increasing eosinophilia. This may reach a very high limit, as in one of Lening's cases, where, three weeks after infection, it had reached 82%. The eosinophilia remains at a high level for a long time, may be for many months, and then gradually [illegible]

comes down as the patient improves, or as a chronic, and more or less tolerant, condition is established.

In November 1912 Bassett-Smith[22] published in tabular form his observations on the blood of a case of Schistosomiasis which came under his care. The disease had been contracted near Hankow, in the Yang-tse valley, in June 1911, and the patient had had to return to England. He steadily improved, and one year after the onset he was apparently well.

	Poly-morpho-nuc.L.	Large mono-nuc.L.	Lympho-cytes.	Eosino-philes.
In September 1911 his blood count showed	36%	12%	14%	38%
In Dec. 1911 " "	20	7	14	59
In Feb. 1912 " "	31	8	16	45

In July 1912 his eosinophile count had come down to 30%, and the patient was feeling quite well. Doubtless the eosinophile count would come down still lower, but the fact that it was still as high as 30% over a year after infection showed that the patient was still reacting to the toxin produced by the living worms in his portal system, although he had become accustomed to their presence, tolerance had become established, and the patient was "feeling quite well".

This may be taken as fairly typical of the differential blood-count in incipient schistosomiasis. In those cases which go on to the severe later stages of the disease, the eosinophilia usually comes down still lower/

lower, and then remains fairly constant. Taking two chronic cases, with livers enlarged to a handsbreadth and more below the costal margin, and abdomens distended with ascitic fluid, I found the blood counts as follows;-

Case 1. Two years duration.		Case 2. Five years duration.	
Polymorphonuclear L.	61%.	Polymorphonuclear L.	52%.
Large Mononuclear L.	16%.	Large Mononuclear L.	12%.
Lymphocytes	7%.	Lymphocytes	24%.
Eosinophile L.	16%.	Eosinophile L.	12%.

If we judge of the condition of the blood only from an enumeration of the blood cells and the percentage of haemoglobin present, the degree of anaemia, though always present to a greater or less extent, would appear, frequently, not to be anything very marked. In Houghton's cases he found the average percentage of haemoglobin to be about 60. The red-cells vary, being frequently between three and four millions per c.mm. The total number of white cells, in uncomplicated cases, is often below the normal number, but here again one cannot speak with any certainty or formulate any fixed rule. In Bassett-Smith's case, mentioned above, the white cells rose from 12,500 per c.mm. in September 1911 to 28,000 in February 1912, and no explanation is given of this leucocytosis. It was apparently incident to the infection.

The degree of anaemia, therefore, as estimated by the haemocytometer and haemoglobinometer would not appear to be of any great moment. I feel, however, that the results/

results which we obtain with these instruments, though they may accurately determine the total number of red cells and the percentage of haemoglobin, do not give us a true idea of the impoverished state of the blood in other respects, or the extent to which it is poisoned by the effete products of the parasite. We have no scientific means by which we can estimate the degree of toxicity of the blood, and can only say that this toxaemia shows itself in a peculiar muddiness of the complexion which is characteristic of these patients, and which is, in itself, highly suggestive of a very impure condition of the blood.

Schistosomiasis in Animals.

Schistosomiasis is a very common disease among the cats and dogs, and other domestic animals, of endemic areas. Lambert[30] states that the foreign sporting dogs, pointers, retrievers, etc., are all, without exception, infected; house dogs which do not go into the water escape infection. The disease in dogs lasts several years, with periods of improvement during the Winter season. The symptoms are those of dysentery - frequent passage of bloody mucus - with much straining, but no ascites. Lambert mentions a previously uninfected pointer bitch which developed high fever and passed bloody stools crowded with eggs of S. japonicum six weeks after her first contact with infected water in the neighbourhood of Kiukiang.

Post-mortem:

Post-mortem examinations on infected dogs, conducted by Lambert and Houghton, revealed pathological changes similar to those found in human beings. There was some chronic peritonitis, great thickening of the coats of the large bowel, and enlargement of the mesenteric lymphatic glands. The worms were found only in the portal and mesenteric veins, not in the arteries, and not in any other veins. By killing a dog with chloroform and opening it up immediately, before the blood had had time to coagulate, numbers of perfect specimens of the worm were removed from the mesenteric veins into normal saline. Eggs were found in large numbers in the submucosa of the large intestine, and in the mesenteric glands.

(I have pleasure in submitting with this Thesis a specimen pair of adult male and female parasites which Houghton was good enough to send me.)

Tsuchiya[14] also published some notes on post-mortem examinations which he made on dogs and cats. In some instances cats were chloroformed, and abdominal section then performed, in order to obtain the worms alive. In the portal and mesenteric veins Tsuchiya could discern the wriggling movements of innumerable parasites. These are readily found if the sectio be undertaken at an acute stage of the disease, but if the case is one of long-standing the worms are not discovered so easily. No trace of worms could be found in vessels other than those of the portal system.

The liver was enlarged in all cases, and its surface roughened/

roughened by tubercles, which, however, were not so large as those found in men. The organ was hard on section and showed nodes of connective tissue, especially in the neighbourhood of branches of the portal vein.

The spleen was generally somewhat enlarged and hard, and of a dark brown colour. The capsule and cut-section showed no change.

The large intestine showed on its serous surface, especially along the mesenteric attachment, a number of greyish-brown tubercles, about the size of a bean. The mucosa presented many greenish spots, but no tubercles. No changes in the small intestine.

The mesenteric lymphatic glands were enlarged and hard and showed white areas on cut section.

The kidneys and bladder were healthy and showed no change.

Microscopic examination.

Liver. The interlobular connective tissue was increased generally, with special proliferation around the portal vein branches, so as to occlude many channels. In this proliferated connective tissue Tsuchiya found round-celled infiltration and eggs. In all cases where eggs were present tissue hyperplasia had developed and consequently vessels had become occluded. "I was not able" Tsuchiya says, "to demonstrate clearly the connection between vessel lumen and eggs, but the eggs must be entombed in portal vein branches, and there are pigment granules scattered round about them." Single eggs

were/

were seen introduced into capillaries in an embolic manner, and eggs were also found in the blood of the portal vein trunk.

Spleen. The spleen sections showed proliferation of connective tissue. The follicles had decreased or entirely disappeared.

In the Mesenteric glands numerous eggs were to be found, partly isolated and partly in crowds with round-celled infiltration round about. Overgrowth of fibrous tissue had developed, as in the liver.

Intestine. Ova were found in the intestinal mucosa, and submucosa. "Once I found some relatively small eggs, the contents of which were granular, and which were grouped in clusters or formed a long row. Round about I noticed round-celled infiltration, with fresh haemorrhage. The other eggs contained embryos and these had caused proliferation of the connective tissue in the neighbourhood. At one place I found the muscular layer of the intestinal wall forced apart by accumulations of eggs." The "small eggs, with granular contents" to which Tsuchiya refers were evidently similar to the ones which I found and have figured and described. As previously stated, I take these to be unfertilized ova which have prematurely escaped from the female worm.

From this account of Schistosomiasis in cats and dogs it will be seen that the disease is very much the same in the domestic animals as it is in the human being. In the latter, however, ascites is a very frequent accompaniment/

accompaniment of the trouble but not in the former. Thomson, writing to me on this point, says "I have known of dogs which have suffered severely for years, but have never known of one to have developed ascites, but, on the contrary, the abdomen becomes more and more retracted; dogs, however, are as a rule destroyed when dysentery and diarrhoea become so severe that shooting becomes more merciful than further attempts at treatment."

DIAGNOSIS.

The diagnosis of Asiatic schistosomiasis, though usually unattended by difficulty, may at times be very obscure, especially for medical men but recently arrived in the East. To one unaccustomed to them, the symptoms of early schistosomiasis are extremely puzzling. The rise of temperature, with the respiratory phenomena, areas of dullness, etc., may excite a suspicion of pneumonia; or the night-fever, followed by sweating, and the cough may lead to a diagnosis of pulmonary tuberculosis. More likely, because the signs and symptoms are not sufficiently definite, the practitioner is not satisfied that it is either the one or the other of the above conditions, and he arrives at the conclusion that he must be dealing with a case of influenza. Or, on account of the diarrhoea and the swinging temperature, he may suspect the case to be one of typhoid fever. The importance/

importance of examining both the blood and the faeces does not occur to him. Were he to do so a flood of light would illumine the obscure problem. In making a differential blood-count he would certainly find a very high degree of eosinophilia, which alone would point, in no uncertain manner, to the possibility that his patient's illness was in the nature of a verminous infection. He would then go on to examine the stools microscopically, and if the sickness had lasted for two or more weeks, there is, even at this early stage, quite a possibility that he would encounter the ova of the parasite. This would of course settle the diagnosis, but even without finding ova, the eosinophilia, if it could not be accounted for by the presence of other parasites, or in any other way, would certainly, and that very clearly, indicate the nature of the trouble. Even though the clinical manifestations of incipient schistosomiasis are by no means constant, the presence of a high grade of eosinophilia, say from 25% to 50%, combined with a history of wading, or bathing, in the waters of an endemic area, and remittent fever, would be sufficient to make the diagnosis practically certain. On this clinical tripod a diagnosis of infection by S. japonicum may be made with confidence.

In later stages of the disease the diagnosis can usually be made without difficulty. The history of the patient, the enlargement of liver and spleen, dysenteric troubles, chronic dyspepsia, ascites, weakness and malnutrition/

malnutrition are all very suggestive, and one's suspicions become confirmed and the diagnosis indisputably established on finding the characteristic ova in the stools.

There is, however, quite an appreciable percentage of cases that are not so readily recognised. These are the unusual and atypical cases. We have, for example, cases which show only a splenic enlargement. There may be no enlargement of the liver, ascites, or bloody stools. Such cases may be difficult to distinguish from other and totally different conditions, as malarial cachexia or Kala-azar. The history, too, and the appearance of the patient, may be misleading and suggestive of the latter maladies. On examining the stools microscopically no ova may be discovered. This is not infrequently the case, for if there is no breaking down of the mucous membrane of the bowel the eggs do not reach the lumen of the gut. It is in such cases as these that a microscopical examination of a blood-smear will be of the greatest service in clearing up the difficulty. Eosinophilia of over 10% is very suggestive of S. japonicum infection, and if the differential count should show that from 25% to 50% or more of the leucocytes are of the eosinophilic variety, the diagnosis will, in the great majority of instances, be established.

The diagnosis may sometimes have to be made from the eosinophilia alone, and this would appear to be especially so in comparatively mild infections of long duration,

other/

other signs being wanting. If, however, the stools be patiently and persistently examined, and sedimentation methods employed, odd ova will frequently be discovered and the diagnosis will become perfectly clear.

There are one or two conditions with which advanced schistosomiasis may be confounded for a time, thus requiring a litte care in the differential diagnosis. These are:-

(a) Splenic anaemia.

In this disease we get a much more profound anaemia than that met with in Schistosomiasis. The spleen is markedly enlarged, but the liver usually only moderately so; thus differing from schistosomiasis, in which, though the spleen is frequently hypertrophied, it is the liver that bears the brunt of the disease, and which shows the most constant and marked enlargement. Later, when cirrhosis of the liver supervenes upon splenic anaemia, and we get the condition known as Banti's disease, with ascites, the diagnosis may be still more difficult; but, even so, the practitioner will find his greatest help in obscure cases in an examination of the blood. The blood in splenic anaemia shows a much greater loss both of red cells and of haemoglobin, and there is, of course, no eosinophilia.

(b) Kala-azar.

In Kala-azar the signs and symptoms may very closely resemble those of Asiatic schistosomiasis.

Here again we have splenomegaly, anaemia, and irregular fever.

fever. The liver may be enlarged, or it may be shrunk and cirrhotic, causing ascites. But the blood-picture will be different and will be sufficient to distinguish the two conditions. In Kala-azar I have always found a very marked leucopenia, a relative large mononuclear increase, and polymorpho-nuclear decrease. There is no eosinophilia, such as one finds in schistosomiasis, though there may be a low grade of eosinophilia due to other verminous parasites. In order to make sure of the diagnosis in cases of Kala-azar I have been accustomed to resort to splenic puncture, and have, as a rule, experienced no difficulty in demonstrating the Leishman-Donovan body.

(c) In other conditions which may simulate schistosomiasis, as chronic malaria with large spleen, or in cirrhosis of liver of other origin, the same test will always be at the practitioner's command, namely, the microscopical examination of the blood. The blood in a malarial patient will, of course, show its own changes, as against those we find in schistosomiasis. Even if no parasites are encountered in the peripheral blood, the presence of pigment, or the high percentage of large mononuclear leucocytes, will make it a comparatively simple matter to recognise cases of malarial infection.

The diagnosis of Asiatic Schistosomiasis is, I repeat, unattended by difficulty in the great majority of cases. Occasionally the practitioner may meet with a case which does not present the usual signs and symptoms/

symptoms, and which, at first, may be obscure and present a little difficulty, and it is on this account that I have made the above remarks regarding the conditions with which the disease is most likely to be confounded.

PROGNOSIS.

In the case of the Chinese boatman or farmer the prognosis is decidedly bad. He is, in all probability, already very heavily infected before presenting himself for treatment, and in any case, from the nature of his occupation, he is liable to be re-infected over and over again. In such a case the disease steadily progresses to a fatal termination.

In the case of foreigners resident in China the out-look is very much more hopeful. The patient will almost certainly consult a medical man for the initial fever which comes on after his first exposure, and, if the physician understands his case, he will be warned from whence the infection was derived. The number of parasites which have effected an entrance into his system is, therefore, likely to be limited. After a varying length of time the symptoms subside, the system gradually becoming more tolerant of the presence of the worms. In all probability the infection is not heavy enough to go on to produce the grosser signs of the disease, such as ascites, and there is this hope, that, in the course of time the parasites will ultimately die out, though probably they are capable of living for a number,

number of years. In the sister condition, Bilharziasis, the eggs of S. haematobium have been found in the urine fifteen or more years after the patient had left Egypt and lived in England. It is not unlikely that S. japonicum, which is so closely related to the African species, can live for a similar length of time. Good health may be enjoyed, however, even though the patient harbours a number of worms, and eggs are passed with the faeces. After an attack of incipient schistosomiasis, normal health is frequently regained in six months. The case of the American boy which Logan described was a fairly severe one, one that had been re-infected on more than one occasion, but even so, he is now doing well in America and is able to compete with his fellows in both bodily and mental exercises. He had no ascites, however. Ascitic cases do badly, showing as they do that irreparable damage has been done to the liver.

The prognosis, of course, depends entirely upon the degree of infection sustained; and upon whether the patient can be safe-guarded from future infection. In the case of foreigners this can usually be done, but it must be remembered that though a foreign patient who has received very heavy infection may improve for a time, yet as the worms live for so long, and as more and more eggs accumulate in the liver, this organ may sustain very serious and permanent damage. In the case of Chinese patients, to guard them from further infection is/

is well-nigh hopeless. In all probability they do not believe the foreign doctor when he tells them the disease is contracted from the water through the unbroken skin, and even were they to believe him, their up-bringing and the conditions of their village life make it practically impossible for them to abandon their daily vocation of fishing or farming, and to seek other means of livelihood.

When we consider the enormous percentage of infected cases in endemic areas, and when we remember that the men go on with their work in the fields as long as their strength will permit, so getting more and more heavily infected, we appreciate something of the terrible amount of suffering and the high mortality which results from this dread disease. It runs its relentless course unchecked, and the patient ultimately succumbs in a state of extreme exhaustion from ascites, toxaemia, and starvation. We have no means of stating exactly what the mortality from schistosomiasis amounts to among the people resident in endemic localities, as there is no such thing as the scientific diagnosis of disease among the native practitioners, and indeed, there is no such thing as the systematic registration of deaths at all.

TREATMENT.

In a verminous infection, such as Schistosomiasis, where the parasites are located, not in the intestinal tract, but in inaccessible portions of the vascular system, the question of treatment becomes an exceedingly difficult one. The ordinary anthelmintics are, of course, useless. Indeed there are no means by which we can dislodge the worms from their secure retreat, and no method is known by which they can be killed within the human body.

There is more hope, perhaps, with regard to the young forms. Now that, given a certain combination of signs and symptoms, we can frequently diagnose Incipient Schistosomiasis, perhaps within a day or two of infection, the treatment might well be directed towards an endeavour to destroy the minute brood while still in its embryonic stage. To this end I have thought sometimes that possibly the prolonged administration of chloroform (inhaled in the usual way, say, for an hour) might be efficacious, but I have never had the opportunity of testing this.

Or, again, some of the organic arsenical compounds might be tried in the hope of destroying the young parasite.

Laning tried both intra-venous and rectal injections of Salvarsan in certain of his cases, but without benefit to his patients. This, however, was not done in the earliest/

earliest stages, not until the worms had, in all probability, reached maturity.

A number of drugs have been tried with the hope of favourably influencing the course of the disease. Dr. Thomson in a private letter tells me of one of his cases, a doctor from one of the gun-boats, who had been out shooting, and had been several times over his waist in the water after wild fowl. He had become infected and showed the usual symptoms with remittent fever, and over 50% eosinophilia. Thomson treated this case with Ext. Felix mas m.30 daily for over a fortnight. Both he and the patient were of the opinion that the rapid improvement which followed this line of treatment was in response to the drug. Exactly what effect this drug has upon the parasite, it would be hard to say. Sandwith[10] states that in the treatment of bilharziasis "the liquid extract of male fern is the only drug of known value, for, though it does not expel the parasites, it seems to weaken their power of doing harm: it diminishes haematuria, allays vesical irritation, and reduces the number of eggs passed in the urine and faeces." It may be that the drug acts in a similar depressant manner on the Asiatic as on the African blood-fluke.

Many other drugs, such as emetine, felicic acid, and urotropin in large doses have been tried, but with no particular benefit.

The/

The treatment of Schistosomiasis must, in the main, be symptomatic.

In incipient cases, cases which are usually met with in foreigners resident in China, the patient should be confined to bed for a few days, and kept on a liquid diet. After the first week the diet may be gradually increased and the patient allowed up in the mornings, when, frequently, he feels better and has more or less interest in the things about him. In the afternoon he will himself take to his bed, as his temperature begins to rise, he feels dizzy, and may be he gets a headache, or abdominal pains. Care should be taken to keep the bowels open. If the patient becomes constipated the abdominal distress becomes much more marked. Laning found magnes. sulphate very useful for relieving the hepatic pain. In Lambert's experience quinine proved useful for the fever, and he thought it influenced the patient's condition favourably. For the headache and backache which accompanies the fever, acetyl-salicylic acid is useful.

Later, when the patient is getting about, liquor arsenicalis and tonics are beneficial, with change of climate and rest. Only slowly will the patient regain his health.

In more advanced cases the patient must still be treated symptomatically. A suitable dietary must be prescribed for the persistent dyspepsia. Saline purgatives and stimulating diuretics are certainly beneficial/

beneficial for the ascites. When this latter condition becomes marked, paracentesis abdominis may have to be performed again and again for its relief. As the collateral circulation by the abdominal wall is frequently very imperfect, and the ascites becomes more and more progressive, Talma's operation, by means of which the omentum is stitched to the curetted abdominal wall so as to produce extensive adhesions and a vascular connection between the portal and systemic vessels, would seem to be indicated. One has to bear in mind, however, the miserable and exhausted physical condition of these patients and that the victims of Asiatic Schistosomiasis make very bad subjects indeed for operative interference of any kind.

PROPHYLAXIS.

The question of prophylaxis is one which is of vital importance to those countries where Schistosome japonicum infection is rife. The suffering and mortality caused by this parasite alone, in China, can hardly be exaggerated. In the infected districts, which are extensive and involve practically the whole of the valley of the lower Yang-tse, it is overwhelming. Many thousands are carried off annually, and many thousands more are rendered unfit for their duties and are hopelessly disabled. In some districts the cases which exhibit the signs of advanced disease, such as extreme ascites, are very numerous. These are young men, or men/

men in the prime of life, who should be the bread-winners of their families, but instead are dependant on their wives and children for support. Many such, borne on stretchers, are brought by their women-folk into our hospitals. When it is considered that in a heavily infected district most of the men, and many of the boys, will be found to be suffering from this disabling condition, and when the high mortality is kept in mind, it will be realised that the problem of this disease is one of great economic importance to China. Malaria is also rife throughout the Yang-tse provinces, as is dysentery (bacterial and amoebic), but serious as these are they are not to be compared, in their disabling powers and in their deadliness, with schistosomiasis.

What then can be done to prevent the spread of this disease? As regards personal prophylaxis, when once the matter is understood, it is simple enough to avoid direct contact of the bare skin with the waters of the ponds, marshes, creeks, and rice-fields in the open country. It may be impossible to say whether any given piece of water is infected or not, but as the disease is so prevalent and the parasite so extensively distributed, the only safe way is to avoid all exposure and so run no risks. Residents in the Yang-tse Valley and other endemic localities should be warned of the danger of wading and bathing, and sportsmen in particular should have the importance of wearing boots

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and puttees impressed upon them.

With regard to prophylaxis on a larger scale, as applied to the native population, the problem is a very much wider and much more difficult one. The task of trying to persuade the Chinese coolie to wear waterproof boots and leggings while at his work in the water would be a futile one; it would be a sheer waste of energy to attempt any such thing. Besides, such a method would not go to the root of the matter. That which is of primary importance is the proper disposal of the excreta. We have already seen that every case of infection by S. japonicum is a source of danger to his fellows. The danger lies in the unseemly habits of the people, who habitually relieve themselves over the sides of their boats, or in the shallow stagnant waters of their rice fields. The eggs of the parasite, passing out in great numbers with the faeces, thus reach water and hatch out in the manner already referred to, and the miracidia swimming actively about are free to invade man.

What can be done to correct this very faulty and undesirable state of things? Katsurada suggests that all excrement should be boiled, but this is, on the face of it, impracticable. We have to think of methods which are capable of being carried out, and the simpler the method the better, provided it be at the same time thoroughly efficient. The great object is to prevent living ova from reaching the water, and it seems to me that

that the only practicable way in which this end can be accomplished to any appreciable extent, is to establish on an extensive scale in the endemic localities a system of dry earth latrines. This is work that might well be taken up by the Government. These latrines need not be large and could be quite economically constructed of wood, with a galvanised iron roof to prevent the entrance of rain water. Inside, defaecation should take place into a dry pit or trench. A plentiful supply of dry earth or sand should be stored under cover of the roof, and this should be used to throw periodically over the surface of the dejecta; or a mechanical contrivance could be employed, by means of which, after use, a quantity of sand could be shot into the pit. It would not be difficult to adjust the details. Under such conditions the embryos could not possibly hatch out, and the eggs would perish. There would of course have to be a sufficient number of latrines for the male population, and many of these would require to be located in readily accessible positions about the rice-fields, and also sufficiently near to the farmers' and coolies' dwellings. From what I have seen of the country people in China I believe that if such latrine accommodation was provided for them, they would be glad to avail themselves of it. I think also that by the use of Government hand-bills and proclamations the people could be educated in the matter. But this must be a question for/

for the future, for at the present the authorities are as ignorant on the subject as the people.

It might be urged against this scheme that the country folk are accustomed, in many places, to store human excrement in other ways, and to use it for fertilizing their fields and vegetable gardens, and that they would not be willing to forego this practice. It is not asked, however, that they should. The ova, as we have seen, very soon perish when dried, and the excreta, having been rendered sterile by the dry earth system in the latrines, could still be employed for use on the land. Animals afflicted by the disease should be destroyed.

CONCLUSIONS.

(1) We have in the Far East (in China, Japan, and the Philippine Islands), a trematode worm known as Schistosoma japonicum, which is specifically distinct from the African species, S. haematobium, and which is parasitic in man.

(2) The invasion of the human body by this parasite produces a terrible and disabling disease of high mortality, Asiatic Schistosomiasis; the signs and symptoms of this disease and the pathological lesions which it causes are characteristic, and perfectly distinct from those of Bilharziasis.

(3)/

(3) Those who are afflicted by this malady are a source of danger to their fellows, inasmuch as the ova of the parasite escape from the body in enormous numbers in the stools. Domestic animals, especially cats and dogs, also become heavily infected and are agents in spreading the disease.

(4) It is essential to the propagation of the parasite that its eggs should speedily reach water of Summer temperature, otherwise they perish and further development is arrested. Hence the disease is contracted only in the Summer months, and occurs only in endemic areas where water is abundant, and where the conditions are suitable for development.

Having reached water, under the required conditions, the embryo hatches from the egg, and a free-swimming ciliated miracidium escapes.

(5) The embryo of S. japonicum, when the opportunity offers, enters through the skin of man and thus infects him. It is obvious that only those who enter the water will become infected. Thus the disease is occupational in origin, and is very prevalent in men and boys living in endemic localities. In China the women escape as they do not go in the water. In Japan the women, who frequently work in the rice-fields, are also infected, though not so much as the men.

(6)/

(6) Having effected an entrance through the skin the parasite gains the lymphatics and thus finds itself carried into the general circulation, and so to the liver, which acts as a nursery for the young forms.

(7) The invasion of the body by Schist. japonicum gives rise to severe febrile reaction, and to all the symptoms which we class under Incipient schistosomiasis.

(8) The worm reaches maturity in the course of three weeks or a month, and migrates from the liver into the portal vein and its tributaries and radicles. Thus it inhabits the veins, and is not found in the arteries of its host.

(9) The severe toxaemia which the parasite gives rise to results in a very marked eosinophilia, and in splenic and hepatic enlargement. The hypertrophy of the liver, in particular, may be very persistent, especially if the patient is periodically re-infected.

(10) The laying of myriads of eggs by the parasite as it lies in the portal vein branches is responsible for untold damage to the living tissues of its host.

(a) In the large bowel the walls become greatly thickened from fibrosis, and the mucous membrane breaks down and ulcerates. Thus dysenteric symptoms form a striking feature of the disease, and it is by way of the necrosed mucosa that the eggs reach the lumen of the gut, and so pass out with the bloody mucoid stools to the exterior.

(b) The mesenteric lymph glands are also seriously affected, as they take up ova which have been carried /

carried to them by the lymphatics from the intestinal walls.

(c) The liver suffers most of all. Owing to the profound toxaemia we have first an inflammatory hyperplasia of the inter-lobular connective tissue, which eventuates in a chronic hypertrophic cirrhosis. The cirrhotic condition is aggravated by the countless ova which reach the liver and plug the portal termini in an embolic manner. As, in the late stages, the fibrous tissue contracts, we get a hard, shrunk-up, nodular organ, further constricting the portal vessels, and very effectually obstructing the portal circulation. In addition to this fibrosis of the liver, the obstruction is sometimes made still more complete by endophlebitis and thrombosis in the portal veins.

(11) Hence it is that the signs and symptoms of the disease are mainly those of portal obstruction, notably chronic venous congestion of the abdominal viscera concerned, gastric trouble and diarrhoea, malnutrition and weakness, and also a persistent and gradually increasing ascites.

(12) The diagnosis is usually unattended by difficulty as the signs and symptoms are characteristic. The court of appeal is the microscope which shows in the blood a remarkably high grade of eosinophilia, and in the faeces the distinctive ova of the parasite.

(13) Foreigners resident in the East must avoid wading and bathing in the waters of endemic districts. This is particularly important in the Yang-tse Valley as the Yang-tse provinces are heavily infected, and the foreign population in the River ports between Hankow and Shanghai is a large one. Sportsmen should be warned /

warned of the danger and recommended to wear boots and puttees.

(14) All infected animals should be destroyed.

(15) Information regarding the mode of infection should be disseminated broad-cast, in the native vernacular. It must be admitted, however, that prophylactic measures as regards the native population would appear at the present time to be well-nigh hopeless. But something might be done if the matter were taken up energetically by Government. A system of dry earth latrines should be insisted upon, instead of the promiscuous deposition of excreta all over the land now in vogue.

Unfortunately the respective governments concerned do not understand the situation, and certainly do not realise that they have any responsibility in regard to the matter. On the other hand, to endeavour to get the rice-planters, boatmen, and coolies to take care of themselves is to court certain disappointment, owing to their ignorance and utter disregard of all warning and advice. But we do not despair. Now that we know something of the natural history of the parasite and its mode of infection, I do not doubt for a moment that the disease is a preventible one, and I look forward to the day when the application of suitable measures shall result in the stamping out of this terrible malady, and another triumph shall be won in the domain of Tropical Medicine.

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